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and

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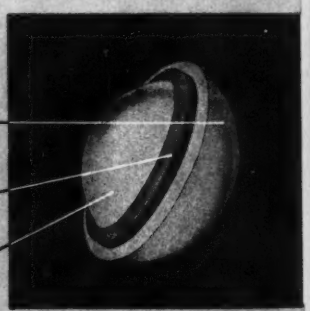

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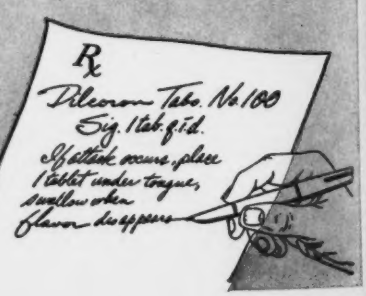

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Circulation

OCTOBER 1960
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AN OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Editorial

Opinions, Decisions, and Facts

MANY of us recall the *New Yorker* cartoon showing the lone figure on the sofa in the midst of a chattering cocktail party. "Oh! He is Doctor Smith," was the explanation. "He doesn't know anything but facts."

Circulation, like other leading medical journals, must be primarily devoted to facts, new, we hope, and the more incontrovertible the better. Opinions, if too easily identifiable, are frowned upon. The experienced contributor disguises his personal views by standard circumlocutions: "It is reasonable to infer...," and "This seems to be consistent with the hypothesis . . ."

This is all proper and admirable. *Circulation* is not designed to be read at cocktail parties. But on most of the important questions discussed in *Circulation,* readers and authors alike do have opinions, which are, of course, the basis for the practical decisions they make every day. The views of those few who write on the great controversial issues are usually discernible behind the formal professions of doubt, but what about the rest of us?

Symposia are devised to smoke out a consensus or to expose the details of disagreement. Even the most democratic of symposia, however, bring into the open the opinions of no more than a handful of discussants. There is little or no machinery in medical science today to gather opinions on a broader basis.

From time to time all of us are subjected to opinion polls of one form or another. Opinion polls are often condemned as merely contributing to the statistics of bias and ignorance. They may be defended as being useful in the evaluation of the trend of the times, including the spread of knowledge, and as possibly revealing the bases on which decisions are made.

In medical science opinion polls are not popular but their equivalent may be represented by the advice physicians give to their patients or, since such information is not easily available, by the sales of drugs sold only on prescription. One approach would be to count the attendance at various scientific sessions according to the topics and the speakers. Another, appropriate to researchers, would be to add up the yearly output of papers or the requests made for research grants on specific subjects.

These last two sources of information scarcely answer the question, "for or against?" a given viewpoint or theory, but by the disclosure of interest at least they allow judgment as to whether the subject has popular appeal to the group in question. (Never mind about deciding whether the appeal is purely intellectual, or directed towards more crass self-interest.)

In any event the fact is that the collection of opinions from responsible physicians and medical scientists is seldom done on any systematic basis. This seems unfortunate in the case of important controversial questions in which it should be valuable to know what opinions are held by persons who must, or should, be influencing the judgment of others less well qualified. Where final answers are

From the Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn.

not at hand (and how often are they?), but decisions are nevertheless required, we ought to know what answers are being given *pro tem.*

Another use of opinion polls is the virtue they may have in forcing people to think. The very act of properly meeting a sensible question must, in any responsible person, promote some consideration, some re-evaluation or rethinking, if the question is one that does not admit of an easy and incontrovertible answer. It is often said that the beginning of wisdom is the recognition of ignorance but this is sterile unless a clear question in some detail is the outcome.

Few questions in modern medical science have aroused so much interest, have such wide implications, and have engendered so much heat and emotion, as that about the interrelationship between the diet, the blood lipids, atherogenesis, and the development of coronary heart disease. Powerful pressures far beyond the ivory tower of the researcher or even the more realistic but still confined world of the physician's consulting rooms, are at work. Not only are the commercial interests immense. Each of us is to some extent the prisoner of his family customs, his personal likes and dislikes in the intimate matter of eating, and the influence of early education, advertising, and the more subtle propaganda of groups concerned to promote "good nutrition."

With all the background and the bewildering profusion of papers on or supposedly related to this subject, what do the readers of *Circulation* think? What do you think and what makes you think so? It is amusing and perhaps useful to consider something like an opinion poll on the subject. A statistical summary of the answers should be interesting but possibly an equally good end would be served if the readers of *Circulation* simply went through the process of answering and reflected on the reason for their answers.

In order to escape the impersonal remoteness of the Gallup Poll, which sometimes seems to suggest a moron asking an ignoramus a foolish question, let us put this in the form of an appeal for consultative advice.

We are concerned about 4 men, all aged 40 and without complaints or clinically detected disease. Repeated measurements show the following:

Subject	Relative weight	Blood pressure	Cholesterol mg. per cent
A	100	130/80	225
B	125	130/80	225
C	100	175/110	225
D	100	130/80	275

1. What, if anything, do you conclude about the relative risk of the future coronary heart disease of subjects B, C, D, compared with Subject A: (Please check)

Subject	Same	2X	4X	6X
B	.....	.....	.....	.....
C	.....	.....	.....	.....
D	.....	.....	.....	.....

2. What, if anything, should these men do? (Please check)

Subject	Nothing	Reduce weight	Treat blood pressure	Reduce cholesterol
B	.....	.....	.....	.....
C	.....	.....	.....	.....
D	.....	.....	.....	.....

3. Can you identify the bases for your answers? (Check if you will)
   Bias ..... Ignorance .....
   Inference from evidence I cannot really cite .....*
   Inference from evidence I am actually able to cite .....
4. Are you willing to be quoted?
   Yes ..... No .....

(*The author will supply a selected list of references if requested.)

ANCEL KEYS

The Evolution of Rheumatic Heart Disease in Children

Five-Year Report of a Cooperative Clinical Trial of ACTH, Cortisone, and Aspirin

A joint report by the Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association.*

Members of the Rheumatic Fever Working Party and United Kingdom participating centers: The late Sir James Spence (Chairman), Royal Victoria Infirmary, Newcastle; Professor A. Bradford Hill, Honorary Director, Statistical Research Unit of the Medical Research Council (Vice-chairman, and Chairman following the death of Sir James Spence); Dr. E. G. L. Bywaters (Secretary), Canadian Red Cross Memorial Hospital, Taplow; Dr. E. Ellis, Royal Victoria Infirmary, Newcastle; Professor Stanley Graham, Royal Hospital for Sick Children, Glasgow; Professor R. S. Illingworth, The Children's Hospital, Sheffield; Dr. B. E. Schlesinger, Hospital for Sick Children, Great Ormond Street, London; Professor A. G. Watkins, Llandough Hospital, Cardiff.

Members of the Principal Investigators Subcommittee and United States participating centers: Dr. David D. Rutstein (Chairman) Coordinating Center, American Heart Association, New York; Dr. Albert Dorfman, La Rabida Jackson Park Sanitarium, Chicago; Dr. Edward E. Fischel, College of Physicians and Surgeons, Columbia University, New York; Dr. John D. Keith, Hospital for Sick Children, Toronto (Canada); Dr. John A. Lichty, University of Colorado Medical Center, Denver; Dr. Benedict F. Massell, House of the Good Samaritan, Boston; Dr. Currier McEwen, New York University-Bellevue Medical Center, New York.

Associated investigators at cooperating centers: In the United Kingdom: Drs. O. P. Gray and N. Royston, Cardiff; Dr. Gavin C. Arneil, Glasgow; Drs. D. G. Cottom, J. N. Montgomery, and H. J. Weston, London; Dr. Rendle Short, Sheffield; Drs. Barbara Ansell, Alan St. J. Dixon, K. Hallidie Smith, and Gerald Thomas, Taplow. In the United States: Drs. Carrol Butler, Florence Mayer, Raymond J. Walther, and Eliot Young, Boston; Drs. John I. Gross, Andrew Lorincz, Irving Rozenfeld, and Katherine Smull, Chicago; Drs. Matthew L. Gibson and John H. Githens, Denver; Drs. Charles W. Frank and Daniel Larson, (Columbia) New York; Drs. Janet Baldwin (deceased), Eugenia F. Doyle, Ann G. Kuttner, Gene H. Stollerman, and Harrison Wood (New York University) New York; Drs. R. D. Rowe and A. D. Barry McKelvey, Toronto (Canada).

Statistical consultation and services were provided by Miss Marjorie T. Bellows, Chief Statistician and Mrs. Elizabeth R. Densen of the American Heart Association and Dr. John Knowelden, London School of Hygiene and Tropical Medicine. Mr. Felix Moore, Professor and Chairman, Department of Public Health Statistics, University of Michigan School of Public Health served as statistical consultant. Dr. A. St. J. Dixon, Taplow served as Coordinating Registrar for the British centers. Mrs. Ruth E. Rutstein was Coordinator for the centers in the United States.

The National Heart Institute of the United States Public Health Service supported the study with grants to the coordinating center and to the cooperating centers in the United States and by a travel grant to the Medical Research Council of Great Britain. The Medical Research Council provided support for the six centers and for a coordinating registrar in the United Kingdom. The center in Toronto received a grant from the Canadian Arthritis and Rheumatism Society. In the United States, the costs of the medical care of its patients were met by each cooperating center, and in Great Britain by the National Health Service. The American Heart Association provided office space for the American Coordinating Center and a grant for statistical services.

This cooperative clinical trial was first proposed by Dr. John R. Mote, then assistant general manager of the Armour Laboratories. For the planning of the study, funds were provided by Armour Laboratories and Merck and Company, and space and services by the Helen Hay Whitney Foundation.

In the planning and conduct of this trial much is owed to the wise advice and guidance of the late Dr. T. Duckett Jones and the late Sir James Spence.

*This report is being published simultaneously in the BRITISH MEDICAL JOURNAL in the United Kingdom, in CIRCULATION in the United States, and in the CANADIAN MEDICAL ASSOCIATION JOURNAL in Canada.

THE UNITED KINGDOM AND UNITED STATES cooperative clinical trial was set up in 1951-52 to compare the relative merits of ACTH, cortisone, and aspirin in the treatment of rheumatic fever and the preven-

tion of rheumatic heart disease. Over a period of approximately a year and a half, and under closely defined diagnostic criteria, 497 children under the age of 16 were admitted to the trial in 12 centers in the United Kingdom, the United States, and Canada. These patients were allocated at random to one or another of the three treatments under investigation. They were treated according to a specified plan for 6 weeks and, after a further 3 weeks of detailed observation, were followed up at defined intervals. Full details of the plan of the study have been given in an earlier publication.[1]

The previous report compared the three treatment groups in detail throughout the 6 weeks of treatment, 3 succeeding weeks of observation, and at the end of a further year of follow-up. It was concluded that there was no evidence that any of the three agents resulted in uniform termination of the disease and on all treatments some patients developed fresh manifestations during treatment. Treatment with either of the hormones had resulted in more prompt control of certain acute manifestations but this more rapid disappearance was balanced by a greater tendency for the acute manifestations to reappear for a limited period upon cessation of treatment. Treatment with the hormones was followed by a more rapid disappearance of nodules and soft apical systolic murmurs. At the end of 1 year, however, there was no significant difference between the three treatment groups in the status of the heart.

This second joint report records the state of the patients after a follow-up of 5 years. It is concerned with a comparison of the amount and severity of rheumatic heart disease in each of the three treatment groups at the end of this time period. It also demonstrates that the status of the heart at start of treatment is the major factor determining the condition of the heart at the end of 5 years and that no treatment can be properly evaluated if this factor is not taken closely into account.

The Numbers Involved

Of the 497 cases admitted to the trial (240 U.K. and 257 U.S.) 445 (89.5 per cent) were known to be alive at the end of the 5 years and the status of the heart had been recorded for all but 19 of them. Sixteen (3.2 per cent) were known to have died. Thus 92.7 per cent of 497 cases had been traced at 5 years. Of the remaining 36 untraced cases 9 were known to be alive at the end of 4 years, 9 at the end of 3 years, 8 at the end of 2 years, 1 at the end of 1 year, and 9 were lost before the end of the first year.

The numbers of deaths and the numbers successfully followed up are given in more detail in table 1, where the cases have been divided into three groups according to the status of the heart on admission to the trial: namely Group A, no or questionable carditis and no pre-existing heart disease; Group B, carditis present but no pre-existing heart disease; and Group C, definite or questionable pre-existing heart disease.*

At the end of 5 years the fact of death or the status of the heart among the survivors had been recorded in 88 per cent in Group A, 90 per cent in Group B and 88 per cent in Group C. Similarly, the figures for the three treatment groups were 91 per cent ACTH, 89 per cent cortisone and 87 per cent aspirin.

*The diagnostic criteria for admission to the study specified carditis as shown by any one of the following:

(a) Development of an organic apical systolic murmur or an aortic diastolic murmur under acceptable observation.

(b) Change of heart size of more than 15 per cent on standard x-ray film by any standard method of measurement.

(c) Pericarditis revealed by a definite friction rub or by pericardial effusion.

(d) Congestive failure, in a patient under 25 years and in the absence of other causes, and shown by one or more of the following: (1) dyspnea, (2) orthopnea, (3) enlargement of the liver, (4) basal pulmonary rales, (5) increased jugular venous pressure, or (6) edema.

In the assessment of carditis as a criterion for entry to the trial, it was assumed in patients with no known pre-existing rheumatic heart disease or history of an attack of acute rheumatic fever, that previous to the current illness the patient's heart was of normal size and that there were no rheumatic murmurs. In other patients observations of changes in heart size and murmurs were used in determining carditis and recorded.

Table 1

Number of Cases Traced at Five Years According to Cardiac Group. U.K., U.S., U.K. and U.S.

Cardiac group at start of treatment	Number of cases					
	At start of treatment	Died	Alive and heart status known	Alive but heart status unknown	Untraced	Per cent untraced
U. K.						
Group A—no or questionable carditis; no pre-existing heart disease	41	0	37	0	4	*9.8*
Group B—Carditis present; no pre-existing heart disease	123	4*	109	4	6	*4.9*
Group C—with definite or questionable pre-existing heart disease	76	7†	61	3	5	*6.6*
All groups	240	11	207	7	15	*6.2*
U. S.						
Group A—no or questionable carditis; no pre-existing heart disease	76	0	66	4	6	*7.9*
Group B—carditis present; no pre-existing heart disease	129	1	112	6	10	*7.8*
Group C—with definite or questionable pre-existing heart disease	52	4	41	2	5	*9.6*
All groups	257	5	219	12	21	*8.2*
U.K. and U.S.						
Group A—no or questionable carditis; no pre-existing heart disease	117	0	103	4	10	*8.5*
Group B—carditis present; no pre-existing heart disease	252	5*	221	10	16	*6.3*
Group C—with definite or questionable pre-existing heart disease	128	11†	102	5	10	*7.8*
All groups	497	16	426	19	36	*7.2*

*One death from acute nephritis and uremia.
†One death from acute intestinal obstruction.

The corresponding figure was 91 per cent for the U.K. and 87 per cent for the U.S.

It is clear that within these classifications no differential losses, which might obscure comparisons, have taken place.

Deaths

Of the 497 children under the ages of 16 who were admitted to the study and completed the prescribed course of treatment only 14 had died from rheumatic fever or rheumatic heart disease by the end of the 5 years of follow-up.* One of these deaths occurred shortly after the end of treatment and 4 more within the first year of follow-up. There were no deaths in the second year and only 1 in the third, followed by 4 deaths in the fourth year and 4 in the fifth. In addition there were 2 deaths from unrelated causes, namely one in the ACTH group from acute nephritis and uremia in the fourth year and one in the cortisone group from acute intestinal obstruction in the fourth year.

Division by treatment of the 14 deaths due to rheumatic fever or rheumatic heart disease shows 7 among the 162 ACTH cases (4.3 per cent), 2 among the 167 cortisone cases (1.2 per cent), and 5 among the 168 aspirin cases (3.0 per cent). Division by cardiac status at the start of treatment (tables 1 and 9) shows no deaths at all in the 117 Group A cases (cases with no or questionable carditis and without pre-existing heart disease), 4 deaths (1.6 per cent) among the 252 Group B cases (carditis

*One child given cortisone who died 20 hours after the start of treatment is not included in the 497 children or the 14 deaths. With this single exception all the patients survived the course of treatment. The death rates following these courses can therefore be compared without the introduction of any bias due to the incidence of deaths during treatment.

present but no pre-existing heart disease) and 10 (7.8 per cent) among the 128 Group C cases (with pre-existing heart disease). Of the Group B cases 1 death occurred among the 37 cases with failure and/or pericarditis at entry (2.7 per cent) and 3 deaths in the remaining 215 cases (1.4 per cent) where these features were absent. Six of the 10 deaths in Group C occurred in a small group of 31 cases where there was already failure and/or pericarditis at the start of treatment. In other words death occurred in 1 out of every 5 of these cases compared with 1 in 25 in the remainder of Group C.

There were more deaths among females (9 in 238 or 3.8 per cent) than among males (5 in 259 or 1.9 per cent) but the difference might very easily be due to chance. There were also more deaths among those whose disease was 6 weeks or more in duration when treatment was started than among those treated within 6 weeks of onset (8 of 104 or 7.7 per cent compared with 6 of 393 or 1.5 per cent). The difference occurred entirely in the Group C cases where the death rate was 17.5 per cent among late treated cases as compared with 3.4 per cent in early treated cases (7 of 40 and 3 of 88 cases). In Group B the rates for late and early treated cases were 1.9 per cent and 1.5 per cent respectively (1 of 54 and 3 of 198 cases). The death rate was not significantly lower among those treated within 2 weeks of onset (3 of 225 or 1.3 per cent) than among those treated at 2 to 6 weeks (3 of 138 or 2.2 per cent).

One of the most remarkable features of this study is the very low case fatality in comparison with previous reports.[2-5] In addition to the modern treatment of the disease there may, however, be a number of other factors concerned in this striking decrease in the severity of the disease. These factors could include a change in the natural history of rheumatic fever or streptococcal infection, the introduction of penicillin and sulfadiazine prophylaxis and environmental features associated with the higher standard of living. There were also six severely ill patients reported in the U.S. as being kept out of the trial of randomized treatments in addition to the one death after 20 hours of treatment (see footnote page 505). On the other hand, not included in this study are cases of rheumatic fever too mild to be admitted to the study hospitals, a number of which limit their admissions to rheumatic fever and receive referrals from other hospitals. In other words the case fatality rate could have been biased in either direction by these selective factors.

Recurrences

The study plan specified that all cases should receive daily prophylaxis with sulfadiazine, after initial eradication of the streptococcus with a 10-day course of penicillin. In spite of this schedule, recurrences did occur and for analytical purposes were defined as the appearance, after an interval of at least 3 months of freedom from rheumatic activity, of manifestations that would have originally qualified the patient for admission to the trial. An analysis was made of all cases retreated for such a recurrence. There were, in total, 64 such retreated recurrences in the 5 years among 56 different cases of the 497 admitted (11 per cent). In addition there were 16 retreated recurrences among 14 cases in which chorea was the only manifestation in the recurrences.

It is more informative, however, to limit attention to the cardiac groups A and B, since many cases in Group C had continuous rheumatic activity making recurrence impossible to identify. In Groups A and B there were, excluding recurrences of pure chorea, 42 recurrences in 36 cases (10 per cent of the 369 cases). Further, in these two groups the 42 recurrences and 36 cases in which they occurred were divided almost exactly among the three treatment groups. Thus, there were 16 recurrences in 12 of the 114 ACTH cases, 12 recurrences in 12 of the 128 cortisone cases, and 14 recurrences in 12 of the 127 aspirin cases. It is clear that the frequency of retreated recurrences does not bias the subsequent comparisons of the treatments used in this study.

Comparison of the Treatments

The dosage schedules of ACTH, cortisone, and aspirin were based on published studies and unpublished reports at that time (1950), the aim being to select a dosage likely to be effective over a period of administration short enough to indicate whether the acute attack had been differentially shortened by any one of the three drugs.

The schedules were as follows:*

ACTH — U.K. cases. A daily dosage in U.S.P. units of 80 for the first 4 days, 60 for the next 3 days, 40 for the second and third weeks, 30 for the fourth and fifth weeks, and 20 for the sixth week.
U.S. cases. 120 U.S.P. units for the first 4 days, 100 for the next 3 days, 80 for the second week, 60 for the third week, 40 for the fourth and fifth weeks, and 20 for the sixth week.

Cortisone — A daily dosage of 300 mg. for the first day, 200 mg. for the next 4 days, 100 mg. for the second and third weeks, 75 mg. for the fourth and fifth weeks, and 50 mg. for the sixth week.

Aspirin — A daily dosage of 60 mg. per pound of body weight or 10 Gm. (whichever was less) for the first 2 days, 40 mg. per pound or 10 Gm. (whichever was less) for the next 5 days, and 30 mg. per pound for the second to sixth weeks.

If retreatment was necessary at any time during the 3 months following the original course of therapy, then a 4-week retreatment scheme was followed using the same drug and dosage as in the first 4 weeks of initial therapy. No patient was retreated unless he demonstrated rheumatic activity sufficient to have brought him into the study initially. If, after 3 months without activity, the patient developed a new attack of rheumatic fever, he was treated as in the original course, i.e., for 6 weeks on the same drug and dosage, followed by a 3-week period of observation.

The results among cases followed for 5 years are analyzed in terms of the cardiac groups already defined.

Looking first at Group A (table 2), it will be seen that 6 of the 37 ACTH cases had a murmur at the end of 5 years (all grade I apical systolic murmurs), 1 of the 33 cortisone treated cases (a basal diastolic murmur), and 1 of the 33 aspirin treated group (a grade I apical systolic murmur). The small excess in the ACTH group is not statistically significant. The striking fact which emerges from this comparison is the exceedingly small proportion of Group A cases treated at these dosage levels of ACTH, cortisone, and aspirin, in which there is evidence of heart disease at the end of 5 years of follow-up. The prognosis in cases without carditis, but otherwise meeting the criteria for the diagnosis of rheumatic fever, is so good that it would be unreasonable to expect that large-dose cortisone therapy could significantly improve it. The well recognized occasional severe toxic manifestations in large-dose cortisone therapy also militate against its use in such cases.[6]

In Group B (table 2), the cases are divided into 6 sub-groups according to their cardiac status, ranging from the mildest with only a grade I apical systolic murmur* to the most severe with pericarditis and/or failure. Examination of these groups shows no consistent difference in favor of any one treatment but the number of cases in each group is small. Direct comparison of the effects of treatment among the total of cases in Group B is not valid because of the unequal distribution of cases of different degrees of clinical severity among the three treatment groups. For example, there were more severely ill cases in the

*Further details of the treatment schedule, including control of auxiliary therapy, can be found in the original report.[1]

*In this study, the following grades were adopted for reporting apical systolic murmurs:

Grade O—No murmur, or a murmur considered to be "functional" on the basis of its apparent origin at the pulmonic area or along the left sternal border.

Grade P—Murmur apparently localized to the apical area, but so faint as not to be transmitted to or toward the axilla. The "P" murmurs were not considered indicative of carditis.

Grade I—Soft apical systolic murmur transmitted to or toward the axilla.

Grade II—Louder similar murmur.

Grade III—Very loud similar murmur, usually transmitted to the back.

Table 2

Number of Cases Followed-up for Five Years and Proportion with One or More Murmurs at That Time, According to Treatment Given and Initial Cardiac Status. U.K. and U.S.

Cardiac group at start of treatment	ACTH			Cortisone			Aspirin		
	No. of cases	With murmurs at 5 years No.	Per cent	No. of cases	With murmurs at 5 years No.	Per cent	No. of cases	With murmurs at 5 years No.	Per cent
Group A—no or questionable carditis; no pre-existing heart disease	37	6	*16*	33	1	*3*	33	1	
Group B—carditis present; no pre-existing heart disease									
1) Apical systolic murmur grade I, only	5	0	*0*	19	3	*16*	15	4	*2*
2) Apical systolic murmur grade II or III, only	18	4	*22*	17	7	*41*	25	8	*3*
3) Apical systolic *and* apical mid-diastolic murmurs	12	9	*75*	15	6	*40*	17	8	*4*
4) Basal diastolic murmur only	3	2	*67*	5	1	*20*	3	0	*0*
5) Basal diastolic *and* other murmurs	16	9	*56*	9	4	*44*	9	5	*56*
6) With failure and/or pericarditis	13	11	*85*	13	8	*62*	7	4	*57*
Group C—with definite or questionable pre-existing heart disease									
1) Without failure and/or pericarditis	26	17	*65*	27	21	*78*	27	18	*67*
2) With failure and/or pericarditis	10	10	*100*	7	7	*100*	5	5	*100*

ACTH group and more of the milder cases in the cortisone group. There were only 5 ACTH in comparison with 19 cortisone cases in the group of mild cases with only a grade I apical systolic murmur. On the other hand, there were 16 cases with a basal diastolic and one or more other murmurs in the ACTH group compared with only 9 in the cortisone group. Also there were only 7 cases with pericarditis and/or failure in the aspirin group in comparison with 13 on ACTH and 13 on cortisone treatment.

It is, however, possible to allow for this unequal distribution of cases of varying degrees of clinical severity among the three treatment groups and thus make a valid evaluation of treatment within the entire Group B. Making the assumption that in each of the cardiac sub-groups the three treatments had no differential effects whatsoever, it is possible to calculate the expected outcome in Group B cases for each of the 3 treatment groups.* The expected figures may then be compared with those which actually occurred. Thus, for ACTH the expected number of cases having murmurs at 5 years was 31 as compared with 35 observed, for cortisone 31 expected versus 29 observed, and for aspirin 30 expected and 29 observed. There is no evidence in this comparison that the prognosis has been affected more by one treatment than by another.

*The proportions with murmurs at 5 years were taken separately for the U.S. and the U.K. for each of 6 sub-groups in Group B *for all three treatments combined.* These proportions were applied to the actual number of patients *on each treatment* and in each of the 6 sub-groups (U.K. and U.S. separately) to see how many in the small sub-groups would have had a murmur at 5 years if they had experienced the total rate of occurrence. The "expected" numbers in each small sub-group were then added to give the total number of Group B cases expected to have murmurs. The numbers expected can then be compared with the observed numbers of cases with murmurs at 5 years.

Table 3

Cardiac Group B (Carditis Present; No Pre-existing Heart Disease). Number of Cases Followed-up for Five Years and Proportion with One or More Murmurs at That Time, According to Treatment Given and Initial Cardiac Status. U.K. and U.S.

Cardiac sub-group at start of treatment	ACTH			Cortisone			Aspirin		
	No. of cases	With murmurs at 5 years No.	Per cent	No. of cases	With murmurs at 5 years No.	Per cent	No. of cases	With murmurs at 5 years No.	Per cent
Group B—carditis present; no pre-existing heart disease									
(1) One murmur, any grade	26	6	*23*	41	11	*27*	43	12	*28*
(2) Two or more murmurs, any grade	28	18	*64*	24	10	*42*	26	13	*50*
(3) With failure and/or pericarditis	13	11	*85*	13	8	*62*	7	4	*57*

An alternative analysis of this important Group B can also be made by comparing separately all cases with a single murmur at the start of treatment and those with two or more murmurs at that time (table 3). Among cases with a single murmur at start of treatment, 23 per cent of those on ACTH, 27 per cent on cortisone, and 28 per cent on aspirin still had one or more murmurs at 5 years, a negligible difference between the treatments. For those who initially had two or more murmurs, the corresponding proportions were 64 per cent ACTH, 42 per cent cortisone, and 50 per cent aspirin. For cases with failure and/or pericarditis at start of treatment the proportions were 85 per cent for ACTH, 62 per cent for cortisone, and 57 per cent for aspirin. In short, in the Group B cases there is no pattern in these results to indicate any advantage for one or another of the forms of treatment.

Finally, of the Group C cases without failure and/or pericarditis at the start of treatment (table 2) there were 26 on ACTH, 27 on cortisone, and 27 on aspirin. At 5 years 17 (65 per cent), 21 (78 per cent), and 18 (67 per cent) had murmurs. Of the 22 Group C cases with failure and/or pericarditis 10 were treated with ACTH, 7 with cortisone, and 5 with aspirin. In every one of these cases murmurs were present at 5 years. There is once again no evidence of any significant difference between the three treatment groups.

The Evolution of Rheumatic Heart Disease

Since there is no evidence that the treatments varied in their effectiveness, the three groups can be added together for the study of the evolution of rheumatic heart disease in this particular series of patients. The essential division is the cardiac status when treatment was begun.

Cardiac Group A

Of the 103 cases in this group 12 (12 per cent) had a murmur at 1 year. At 5 years* (table 4) the figure is 8 or 8 per cent (7 with grade I apical systolic murmur and 1 with a basal diastolic murmur). It appears that the outlook is better for the 71 cases without any murmur than for the 32 with a questionable murmur† at the start of treatment, 96 per cent with no apparent heart disease compared with 84 per cent. The difference is not formally

*Murmurs in all cardiac groups both appeared and disappeared in the time interval between 1 and 5 years. Thus in some cases murmurs present at 1 year were absent at 5 years, while in other cases that were without murmurs at 1 year a murmur was present at 5 years.

†The questionable apical systolic murmur (P murmur) was defined differently in the United States than in the United Kingdom. This difference affects the comparison of the results between the countries and the interpretation of the natural history of the disease. In the U.S., each principal investigator was permitted to classify a doubtful apical systolic murmur as a P murmur. In the U.K., however, the Working Party agreed that each investigator make a firm decision as to the presence or absence of an apical systolic murmur at the time of admission of the cases to the study. (A few cases, 7, were called doubtful in the U.K.). In the U.K. some patients with doubtful apical systolic murmurs were unquestionably labelled "no murmur," others were labelled "apical systolic murmur" and included in Group B.

Table 4

Cardiac Group A (No or Questionable Carditis; No Pre-existing Heart Disease). Number of Cases Followed-up for Five Years and Proportion with One or More Murmurs at That Time. U.K., U.S., U.K. and U.S.

Cardiac sub-group at start of treatment	U. K.			U. S.			U. K. and U. S.		
	No. of cases	With murmurs at 5 years No.	Per cent	No. of cases	With murmurs at 5 years No.	Per cent	No. of cases	With murmurs at 5 years No.	Per cent
Group A—no or questionable carditis; no pre-existing heart disease	37	6	*16*	66	2	*3*	103	8	*8*
No murmur	30	3	*10*	41	0	*0*	71	3	*4*
Questionable murmur*	7	3	*43*	25	2	*8*	32	5	*16*

*A murmur apparently localized to apical area but so faint as not to be transmitted to or toward axilla.

significant but it appears in both countries and is in accordance, as shown later, with the general trend of the results.

The number of retreated recurrences in Group A was 10, but none of the 9 cases followed for 5 years had a murmur at that time.

In summary, the prognosis for the cases without carditis when treatment is started (Group A) is excellent. None of the patients had died and 92 per cent were without apparent heart disease 5 years later.

Cardiac Group B

Of the 252 cases in this category originally admitted to the study 5 had died, 10 were known to be alive although their cardiac status was unknown, and the cardiac status at 5 years had been recorded for 221. The remaining 16 had been lost (table 1). As has already been shown the group is clinically heterogeneous and for analysis of the 5-year results has been subdivided in table 5 into five sub-groups of murmurs (without failure and/or pericarditis) and one sub-group comprising cases with failure and/or pericarditis. The untraced cases were spread evenly over these sub-groups. Confining attention first of all to the total figures (U.K. and U.S.) the following results may be noted:

(1) Cases with a Grade I Apical Systolic Murmur Alone

Of the 39 cases with only a grade I apical systolic murmur at the start of treatment 14 or 36 per cent had murmurs at 1 year while at 5 years the number had fallen to 7 or 18 per cent (3 with a grade I apical systolic murmur, 1 with a grade III apical systolic murmur, 1 with apical systolic and mid-diastolic murmurs, 1 with basal diastolic, apical systolic and mid-diastolic murmurs, and 1 with apical systolic and pre-systolic murmurs). Thus 82 per cent of this group had no apparent heart disease at 5 years and none had died.

(2) Cases with a Grade II or III Apical Systolic Murmur Alone

Of the 60 cases in this category 32 or 53 per cent had at least one cardiac murmur at 1 year. This figure had decreased considerably at 5 years to 19 or 32 per cent (6 with grade I apical systolic murmurs, 5 with grade II or III apical systolic murmurs, 5 with apical systolic and mid-diastolic murmurs, 1 with basal diastolic and apical systolic murmurs, and 2 with known but unspecified murmurs). Thus among these cases 68 per cent had no apparent heart disease at 5 years. Two additional cases originally in this group had died, both in the first year.

(3) Cases with an Apical Systolic Murmur of Any Grade Plus an Apical Mid-Diastolic Murmur

Of the 44 cases in this category 28 or 64 per cent had at least one murmur at 1 year while at 5 years the number was 23 or 52 per cent (6 with an apical systolic murmur grade I, 6 with an apical systolic murmur grade II or III, 4 with an apical systolic and an apical mid-diastolic murmur, 2 with a basal diastolic murmur and an apical systolic murmur, 3

Table 5

Cardiac Group B (Carditis Present; No Pre-existing Heart Disease). Number of Cases Followed-up for Five Years and Proportion with One or More Murmurs at That Time. U.K., U.S., U.K. and U.S.

Cardiac sub-group at start of treatment	U. K.			U. S.			U. K. and U. S.		
	No. of cases	With murmurs at 5 years No.	Per cent	No. of cases	With murmurs at 5 years No.	Per cent	No. of cases	With murmurs at 5 years No.	Per cent
Without failure and/or pericarditis	97	36	*37*	91	34	*37*	188	70	*37*
1) Apical systolic murmur grade I, only	14	4	*29*	25	3	*12*	39	7	*18*
2) Apical systolic murmur grade II or III, only	28	10	*36*	32	9	*28*	60	19	*32*
3) Apical systolic *and* apical mid-diastolic murmurs	24	11	*46*	20	12	*60*	44	23	*52*
4) Basal diastolic murmur only	6	1	*17*	5	2	*40*	11	3	*27*
5) Basal diastolic *and* other murmurs	25	10	*40*	9	8	*89*	34	18	*53*
With failure and/or pericarditis	12	10	*83*	21	13	*62*	33	23	*70*

with a basal diastolic murmur, an apical systolic, and a mid-diastolic murmur, and finally 2 with an apical pre-systolic murmur accompanied by an apical systolic murmur in the first and by an apical systolic and a basal diastolic murmur in the second). Thus, among these cases only about half (48 per cent) had no apparent heart disease at 5 years. In addition one had died during the fourth year but not from rheumatic fever.

(4) Cases with a Basal Diastolic Murmur Alone

There were only 11 cases in this category of whom 5 or 45 per cent had at least one murmur at 1 year, decreasing to 3 cases or 27 per cent at 5 years (2 with basal diastolic murmurs alone, 1 with unspecified murmurs). Thus, 73 per cent of this group had no apparent heart disease at 5 years. None had died.

(5) Cases with a Basal Diastolic Murmur and an Apical Systolic and/or a Mid-Diastolic Murmur

Of the 34 cases in this category at 5 years, 33 were reported at 1 year and of these, 22 or 67 per cent had at least one murmur at that time. The figure decreased to 18 out of 34 cases or 53 per cent at 5 years (4 with a grade II apical systolic murmur, 1 with apical systolic and mid-diastolic murmurs, 1 with an apical mid-diastolic murmur alone, 7 with a basal diastolic murmur alone, and 5 with a basal diastolic murmur and another murmur, 4 of which were apical systolic and 1 a mid-diastolic murmur). Thus, almost one half of this group (47 per cent) had no apparent heart disease at 5 years. In addition one patient had died during the fifth year.

(6) Cases with Failure and/or Pericarditis

Turning finally to the cases in Group B with failure and/or pericarditis at the start of treatment, there were 33 such cases, of which 24 or 73 per cent had at least one murmur at 1 year. At five years 23 or 70 per cent had a murmur (4 with a grade I apical systolic murmur, 8 with a grade II or grade III apical systolic murmur, 3 with apical systolic and mid-diastolic murmurs, 2 with a basal diastolic murmur alone, and 6 with a basal diastolic murmur and other murmurs of which 3 were apical systolic, 2 were apical systolic and mid-diastolic, and 1 was apical pre-systolic and mid-diastolic). In other words, only 30 per cent of this group were without apparent heart disease at 5 years. In addition one patient had died during the fourth year.

Comparison of the U.K. and U.S. experiences in all Group B cases (table 5) reveals no consistent pattern of advantage or disadvantage. The largest difference, which lies in the group with basal diastolic plus other murmurs, is almost entirely a function of a

Table 6

Cardiac Group B (Carditis Present; No Pre-existing Heart Disease). Number of Cases Followed-up for Five Years and Numbers Expected and Observed to Have Murmurs at Five Years According to Sex, Age, Duration from Onset, and Presence or Absence of Various Signs or Symptoms. U.K. and U.S.*

Status at start of treatment	Number of cases	Number with murmurs at 5 years	
		Observed	Expected*
Males	104	41	44
Females	117	52	49
Under 10 years of age	119	55	54
10-16 years of age	102	38	39
0-14 days from onset	102	38	39
15 + days from onset	119	55	54
P-R .18+	54	15	20
P-R <.18	167	78	73
With joint involvement	76	26	30
Without joint involvement	145	67	63
With nodules	38	20	17
Without nodules	183	73	76
With chorea	30	8	11
Without chorea	191	85	82

*Expected numbers take account of differences in the severity of cardiac involvement among the groups being compared. They were calculated in the following manner: The proportions of cases with murmurs at 5 years were taken separately for the U. S. and the U. K. for each of the six cardiac sub-groups in Group B. These proportions were applied in the U. S. and U. K. separately to the actual number of patients in each cardiac sub-group of the categories listed above to see how many in the small sub-groups would have had a murmur at 5 years if they had experienced the total rate of occurrence. The "expected" numbers in the sub-groups were added to get the total number expected in each category for the U. S. and U. K. combined.

differing standard of interpretation, since the U.K. figure is derived from one center only. Thirty of the total 31 U.K. cases with a basal diastolic murmur at start of treatment whose status was known at 5 years were reported from this center. The basal diastolic murmurs in cases at this center were soft and 25 of the 30 disappeared.

An analysis was made of other factors which might have prognostic effects. These included sex, age, duration from onset, and presence or absence at start of treatment of polyarthritis, nodules, chorea, and prolonged P-R interval. None of these individually appeared to affect the evolution of rheumatic heart disease as measured by the presence of murmurs at 5 years (table 6). Cardiac enlargement as measured by a cardiothoracic ratio on the teleroentgenogram of 0.60 or greater was present at start of therapy in 16 Group B cases. In 13 of these at least one murmur was present at 5 years. This serious prognosis is explained by the large number of such cases (11 of 16) that had cardiac failure and/or pericarditis at start of treatment, practically all of which (10 of 11) had at least one murmur at 5 years.

Retreated recurrences occurred in 25 Group B cases. The cardiac status at start of treatment among these cases was, on the average, more severe than in the remainder of Group B cases (table 7). At 5 years these retreated patients had a larger proportion with murmurs than those without retreated recurrences. However, the relationship between cardiac status at start of therapy and at 5 years still held even though retreated attacks had occurred in the interim. Among Group A cases there were no murmurs at 5 years in 9 cases with retreated recurrences; in Group B cases with a single murmur at start of treatment 3 out of 8 cases had murmurs at 5 years as compared with 9 out of 9 in cases with two or more murmurs and 7 out of 8 cases with failure and/or pericarditis.

Summarizing the cases with carditis but without pre-existing heart disease (Group B), it is clear that prognosis is directly dependent on the amount and severity of cardiac involvement at the start of treatment, the proportion with a murmur at 5 years varying from 18 per cent in those with a grade I apical systolic murmur to 70 per cent among those with pericarditis and/or failure. Excluding the group with basal diastolic murmurs for the reason given above and because of the relatively few cases in this category in the U.S., this trend holds when the figures are examined individually for each country. In addition, the proportion of all Group B cases with murmurs is remarkably similar in the two countries

Table 7

Cardiac Group B (Carditis Present; No Pre-existing Heart Disease). Number of Cases with and without Retreated Recurrences Followed-up for Five Years and Proportion with One or More Murmurs at That Time. U.K. and U.S.

Cardiac sub-group at start of treatment	Without retreated recurrences			With retreated recurrences		
	No. of cases	With murmurs at 5 years No.	Per cent	No. of cases	With murmurs at 5 years No.	Per cent
Group B—carditis present; no pre-existing heart disease						
1) One murmur, any grade	102	26	*25*	8	3	*38*
2) Two or more murmurs, any grade	69	32	*46*	9	9	*100*
3) With failure and/or pericarditis	25	16	*64*	8	7	*88*

Table 8

Cardiac Group C (Definite or Questionable Pre-existing Heart Disease). Number of Cases Followed-up for Five Years and Proportion with One or More Murmurs at That Time. U.K., U.S., U.K. and U.S.

Cardiac sub-group at start of treatment	U. K.			U. S.			U. K. and U. S.		
	No. of cases	With murmurs at 5 years No.	Per cent	No. of cases	With murmurs at 5 years No.	Per cent	No. of cases	With murmurs at 5 years No.	Per cent
Without failure and/or pericarditis	45	36	*80*	35	20	*57*	80	56	*70*
With failure and/or pericarditis	16	16	*100*	6	6	*100*	22	22	*100*

Table 9

Prognosis in Relation to Cardiac Status at Start of Treatment. U.K. and U.S.

Cardiac status at start of treatment	No. of cases observed for 5 years	Per cent with no murmur at 5 years	No. of deaths in 5 years
Group A			
No carditis	71	*96*	0
Questionable carditis	32	*84*	0
Group B			
Apical systolic murmur grade I, only	39	*82*	0
Apical systolic murmur grade II or III, only	60	*68*	2
Apical systolic *and* apical mid-diastolic murmurs	44	*48*	1†
Basal diastolic with or without other murmurs	45 (15)*	*53 (27)**	1
Failure and/or pericarditis	33	*30*	1
Group C			
Pre-existing heart disease without failure and/or pericarditis	80	*30*	5‡
Pre-existing heart disease with failure and/or pericarditis	22	*0*	6

*Excluding one U. K. center.

†Death from acute nephritis and uremia.

‡Includes 1 death from acute intestinal obstruction.

Cardiac Group C

There were 102 cases with known cardiac status at 5 years who had definite or questionable pre-existing heart disease at the start of their treatment (table 8). Of the 80 without failure and/or pericarditis at start of treatment, 70 per cent had heart disease at 5 years and of the 22 with failure and/or pericarditis, all had heart disease. It may also be recalled that in addition 4 and 6 deaths from rheumatic fever had taken place respectively in these two groups and one death from other causes in the group without failure or pericarditis.

* * * *

In table 9 all of the cases in the study followed for 5 years are listed in the order of increasing severity of heart disease at start of treatment. It is abundantly clear that the range from 96 per cent to 0 per cent with normal hearts at 5 years is much more striking than differences reported here or ascribed elsewhere to the effects of treatment. Thus, in the prevention of rheumatic heart disease no evaluation of therapy of acute rheumatic fever can be valid unless this major factor is taken into account in the design of the study or the analysis of the data. This conclusion is reinforced by the occurrence of most of the deaths from rheumatic fever (10 of 14) among cases with pre-existing heart disease, and the absence of deaths among the cases without heart involvement at start of treatment.

No comparisons have been made with the conflicting reports of results obtained with large-dose hormone therapy[7–11] the most recent of which shows no advantage in a well controlled study.[11] A firm decision on the efficacy of large-dose hormone treatment of rheumatic fever will depend on controlled studies of adequate size in which the status of the heart is taken into account.

Summary

1. A study has been made 5 years after the end of treatment of the 497 children who were admitted to the U.K./U.S. cooperative clinical trial of the relative merits of ACTH, cortisone, and aspirin in the treatment of acute rheumatic fever.

2. Four hundred and forty-five of the cases (89.5 per cent) were followed for the complete 5 years and the status of the heart was known for 426 of them. Only 16 (3.2 per cent) had died, 14 of them from rheumatic heart disease; 36 (7.2 per cent) were untraced. The very low fatality rate is striking.

3. At the end of 5 years, there is no evidence that, on the treatment schedule used in this study, the prognosis has been influenced more by one treatment than another. This confirms the findings reported at 1 year.

4. The major factor in determining the incidence of rheumatic heart disease at the end of 5 years is the status of the heart at the time treatment was begun. For cases without carditis initially the prognosis was excellent, since in 96 per cent there was no residual heart disease. In cases with carditis initially but without pre-existing heart disease the proportion without residual heart disease decreased progressively from 82 per cent for those with only a grade I apical systolic murmur to 30 per cent for those with failure and/or pericarditis. In cases with pre-existing heart disease the prognosis was poor. Only 30 per cent of those without pericarditis or failure and none of those with pericarditis and/or failure were without heart disease at 5 years.

5. Cases with carditis and without pre-existing heart disease which had recurrences demanding retreatment during the follow-up period had on the average a more severe cardiac status at start of treatment than did those without recurrences requiring retreatment. At 5 years a larger proportion of these retreated cases had murmurs.

6. These results make clear that treatment of acute rheumatic fever cannot be properly evaluated unless the status of the heart of the patients at the start of treatment is taken closely into account.

Summario in Interlingua

1. Esseva studiate 5 annos post le completion de tractamento del 497 juveniles includite in le essayo clinic cooperative del Regno Unite e del Statos Unite

relative al meritos comparative de ACTH, cortisona, e aspirina in le tractamento de acute febre rheumatic.

4. Quatro centos quaranta-cinque del casos (89,5 pro cento) esseva observate durante le complete periodo de 5 annos, e le stato del corde esseva cognoscite in 426. Solmente 16 (3,2 pro cento) habeva morite, con morbo rheumatic del corde como causa mortal in 14. Trenta-sex (7,2 pro cento) mom poteva esser traciate. Le bassissime mortalitate es frappante.

5. Al fin de 5 annos, le datos non indica que—sub le conditiones de tractamento usate in iste studio—le prognose esseva influentiate plus marcatemente per un del formas de tractamento que per le alteres. Isto representa un confirmation del constatationes al fin del prime anno.

4. Le plus importante factor de determination pro le incidentia de morbo cardiac rheumatic al fin del 5 annos es le stato del corde al tempore quando le tractamento esseva initiate. Pro casos sin carditis al initio, le prognose esseva excellente, proque in 96 pro cento de istos il habeva nulle residue morbo cardiac. In casos con carditis al initio sed sin pre-existente morbo cardiac, le proportion del disparition complete de morbo cardiac declinava progressivemente ab 82 pro cento in le gruppo con solmente un murmure apico-systolic de grado 1 a 30 pro cento in le gruppo con disfallimento e/o pericarditis. In casos con pre-existente morbo cardiac le prognose esseva mal. Solmente 30 pro cento del subgruppo sin pericarditis o disfallimento e nulle del subjectos in le gruppo con pericarditis e/o disfallimento esseva libere de morbo cardiac al fin del 5 annos.

5. Le casos con carditis e sin pre-existente morbo cardiac le quales habeva recurrentias que requireva un retractamento durante le periodo de observation habeva habite—a generalmente parlar—un plus grave stato cardiac al initio del tractamento que le casos sin recurrentias a character requirente re-tractamento. Al fin del 5 annos, murmures esseva presente in un plus grande proportion de ille casos retractate.

6. Iste resultatos rende clar que le tractamento de acute febre rheumatic non pote esser evalutate adequatemente si le stato del corde del patiente al comenciamento del tractamento non es prendite in consideration in omne su aspectos.

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Catecholamines in the Localization of Pheochromocytoma

By J. Richard Crout, M.D., and Albert Sjoerdsma, M.D., Ph.D.

THE MEASUREMENT of norepinephrine and epinephrine in urine and plasma provides a reliable basis for the diagnosis of pheochromocytoma.[1, 2] Previous work[1, 3] has suggested that these assays may also be helpful in defining the location of the tumor in the body, thereby facilitating successful surgical treatment. In 6 cases of pheochromocytoma von Euler[3] noted a correlation between the type of amine excreted in the urine and the location of the tumor: 3 patients excreted increased amounts of epinephrine as well as norepinephrine and had tumors of the adrenal regions, while the other 3 excreted norepinephrine alone and had tumors in extra-adrenal sites. In a later review of 35 cases of pheochromocytoma, however, von Euler and Ström[1] noted several exceptions to this general correlation between the type of amine excreted and the location of the tumor. They concluded that the differential catecholamine assay in urine provided only suggestive evidence of tumor location. More precise information concerning the tumor site was obtained by catheterizing the venae cavae and demonstrating an increase in plasma catecholamine concentration at the level of venous drainage from the tumor.[1, 4]

To evaluate the practical usefulness of these approaches for localizing pheochromocytomas, we have reviewed our own and other data on urinary catecholamine excretion. In addition, we have performed 6 venous catheterizations in 5 patients with pheochromocytoma to determine the plasma catecholamine concentration at various locations within the great veins. The results indicate that both procedures may be distinctly helpful under selected circumstances in the preoperative localization of the tumor.

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Materials and Methods

Twenty-four-hour urine specimens obtained from 18 patients with pheochromocytoma were assayed for free norepinephrine and epinephrine by a modification[5] of the fluorimetric method of von Euler and Floding.[6] The catecholamine content of pheochromocytoma tissue was determined by homogenizing a portion of tumor in trichloroacetic acid and assaying the supernatant colorimetrically or fluorimetrically.[7] Epinephrine values were considered to lack quantitative significance when they were less than 10 per cent of the norepinephrine figure.

Vena caval catheterization was performed in 5 cases through either an antecubital or saphenous vein. Blood samples were obtained at various sites within the venae cavae as the catheter was withdrawn and repositioned under fluoroscopic control. The specimens were drawn approximately at 3-minute intervals on any single passage up or down the venae cavae. The blood samples (20 to 30 ml.) were collected in heparinized syringes and stored in ice until the procedure was completed. Plasma obtained after centrifugation was assayed fluorimetrically for catecholamines (as norepinephrine equivalents) by the ethylenediamine condensation procedure of Weil-Malherbe and Bone.[8]

Results

The results are given in two sections: the first presenting data on urinary catecholamine excretion and tumor location in the entire series of patients, and the second describing in detail the case histories of 5 patients upon whom vena caval catheterizations were performed.

Urinary Catecholamines and Tumor Location

The values for free urinary norepinephrine and epinephrine in 18 cases of pheochromocytoma are shown in table 1. In cases 1 to 14 norepinephrine was the predominant catecholamine in the urine; the epinephrine value in each case was less than 10 per cent of the norepinephrine excretion. Eleven of these patients had tumors of the adrenal gland and the remaining 3 had tumors in nonadrenal sites. Cases 15 to 18 showed a significant elevation of epinephrine as well as of norepi-

Table 1

Urinary Excretion of Free Catecholamines and Location of the Tumor in Eighteen Patients with Pheochromocytoma

Case no.*	Norepinephrine (μg./day)	Epinephrine (μg./day)†	Location of tumor
1	310	I	Right adrenal
2	320	I	Right adrenal
	700	I	
3	97‡	I	Right adrenal
4	1510	I	Right adrenal
5	930	I	Left adrenal
6	1590	I	Left adrenal
7	3800	I	Right adrenal
8	620	I	Bilateral adrenal tumors
9	820	I	Right adrenal
10	260	I	Left adrenal
	170	I	
11	740	I	Right adrenal
12	3000	I	Generalized metastases, presumably from adrenal tumor removed 2 years previously.
13	880	I	Behind inferior vena cava, medial to right adrenal.
14	2700	I	Right side of neck
15	690	280	Right adrenal
	310	220	
16	42	36	Left adrenal
17	1030	510	Right adrenal
18	690	110	Surrounding aorta at origin of inferior mesenteric artery (organs of Zuckerkandl)
Normal	10-70	0-15	

*Cases 1, 3, and 12 have been reported independently by Sunderman and Sunderman,[9] cases 8 and 14 by Cone and associates,[10,11] and case 6 by Greenberg and Gardner.[12]

†I-insignificant; i.e., less than 10 per cent of the norepinephrine value.

‡Incomplete specimen, representing excretion during a period of about 8 hours.

nephrine in the urine. Three of these patients had tumors of the adrenal glands and the fourth had a tumor of the organs of Zuckerkandl.

A review of the literature covering the period from 1950 through June 1959 revealed 61 additional cases of pheochromocytoma with sufficient data to correlate urinary norepinephrine and epinephrine excretion with the tumor site. Thirty-two of these cases were from the series of von Euler and Ström,[1] and 29 were from individual case reports.[13-35] The 79 cases were divided into 2 groups: (1) those in which the excretion of both norepinephrine and epinephrine was significantly elevated and (2) those in which only norepinephrine was increased, epinephrine accounting for less than 10 per cent of the catecholamine excretion (table 2). Thirty-three patients had tumors producing significant amounts of epinephrine, and 31 of these had tumors located in the adrenal areas. Only 2 cases of a nonadrenal tumor producing significant amounts of epinephrine have been reported (case 18, table 1),[18] and in both of these the tumor originated from the organs of Zuckerkandl. Forty-six patients had tumors that secreted only norepinephrine in significant amounts. Thirty-one of these had tumors of the adrenal area, the remainder having extra-adrenal tumors varying in location from the lower abdomen to the neck.

Table 2

*Urinary Catecholamines and Tumor Location in Seventy-nine Cases of Pheochromocytoma**

Location of Tumor	Elevated Urinary Norepinephrine and Epinephrine		Elevated Urinary Norepinephrine Only	
Adrenal Areas:				
Right	17		20	
Left	12		9	
Bilateral	0		2	
Side not specified	2		0	
Total		31		31
Non-adrenal Areas:				
Organs of Zuckerkandl†	2		6	
Along aorta (other than in organs of Zuckerkandl.)	0		3	
Paravertebral lumbar	0		2	
Thorax	0		1	
Neck	0		1	
Generalized spread	0		2	
Total		2		15
Total tumors		33		46

*References 1, 13-35, and present series (table 1).

†The organs of Zuckerkandl are located on either side of the aorta near the base of the inferior mesenteric artery.[36] All tumors described as located "along the aorta at the level of the duodenum" or "between the lower poles of the kidneys" are also included in this category.

Case Reports and Catheterization Studies

Descriptions of each of the 5 cases in which vena caval catheterizations were performed are presented individually, and the results of the catheterization procedures are summarized in table 3.

Case A

C. R., (case 14, table 1[10]), an 8-year-old white boy was admitted to the National Naval Medical Center, Bethesda, Maryland, in August 1957 because of hypertension and a mass in the right side of the neck. Two years previously a pheochromocytoma had been removed from the right adrenal area. Following this operation he was normotensive and in good health until 5 months prior to admission, when the cervical mass was first noted. Recurrence of hypertension was discovered 3 weeks before admission.

The patient's maternal aunt and her son had both had pheochromocytomas, and the patient's mother (case E) was later found to have a pheochromocytoma.

The physical examination revealed a blood pressure of 155/120 mm. Hg, Horner's syndrome on the right, and a 4 by 4 cm. firm, nontender mass in the right submandibular region. The catecholamine excretion after acid hydrolysis of the urine was on 2 occasions 1,750 and 2,680 μg. per day of norepinephrine. The free catecholamine excretion in a third specimen was 2,700 μg. per day of norepinephrine. No significant amount of epinephrine was found in the urine.

Since no instance of a cervical pheochromocytoma had been reported prior to this case, the question arose as to whether the submandibular mass was a pheochromocytoma or whether it was an unrelated tumor associated with a pheochromocytoma in the abdomen. Massage of the mass produced a slight increase in the blood pressure, which was difficult to interpret. The vena cava was catheterized through a right antecubital vein, and blood samples were drawn at 4 levels within the venae cavae (table 3). The catecholamine concentration was markedly elevated in each sample, but the highest values were found in samples obtained from the superior vena cava, suggestive of a cervical pheochromocytoma. The highest single plasma level was found not high in the superior vena cava as anticipated but low in the superior vena cava, near the right atrium. Possible explanations for this finding included a higher secretion rate by the tumor at the time the low superior vena cava sample was drawn, poor sampling high in the superior vena cava due to a "streaming effect," or the presence of a second pheochromocytoma in the thorax draining via the azygous vein. However, no tumor could be visualized by roentgenography of the chest. The cervical tumor was subsequently removed and found to be a 15-Gm. pheochromocytoma containing 5.0 mg. per Gm. of norepinephrine but no detectable epinephrine.

The catheterization was of value in indicating that the cervical mass was indeed a pheochromocytoma, in spite of the unusual location. Definitive surgical therapy could thus be undertaken without subjecting the patient to further diagnostic procedures in search of a pheochromocytoma in the abdomen.

Case B

H. F., (case 13, table 1), a 40-year-old Negro man was admitted to the National Heart Institute in July 1958 because of hypertension. In 1949 a pheochromocytoma was suspected because of hypertension. During an exploration of the right adrenal area the patient developed acute pulmonary edema and the operation was terminated in-

Table 3

*Plasma Catecholamines at Various Sites within the Venae Cavae in Five Patients with Pheochromocytoma**

Case	Sampling series	Plasma norepinephrine-equivalent (μg./L.) High SVC†	Low SVC	High IVC	Low IVC	Average blood pressure (mm. Hg)	Location of tumor
A	1	49	69	32	23	140/100	Neck
B (first	1	23	22	21		200/120	Behind
cath.)	2		21	14		200/120	vena cava
	3			41	15	190/120	medial to right
(second	1		20	9	12	168/116	adrenal
cath.)	2			14	13	174/124	
	3			70	18	170/110	
C	1			31	12	164/98	Right
	2	16	18	13	17	180/106	adrenal
D	1		20	45, 46	16, 16	140/104	Right
				31	(left flank massage)		adrenal
				38	(right flank massage)		
E	1	8	11	8	7	160/100	Left
	2‡		4	7		160/100	adrenal
	3		5	4	4	140/90	
Normal		1-6 μg./l					

*Underlined values considered to represent significant "step-ups" in plasma catecholamine concentration.

†High SVC, superior vena cava near the junction of the innominate veins; low SVC, superior vena cava near the right atrial junction; high IVC, inferior vena cava near the right atrial junction; low IVC, inferior vena cava near the iliac bifurcation.

‡Following the intravenous injection of 0.025 mg. of histamine.

mediately. Later in 1949 bilateral exploration of the adrenal regions did not reveal a tumor. Because of continuing hypertension a bilateral thoracolumbar sympathectomy was performed in 1950 and again a tumor was not found along either sympathetic chain. For the following 8 years he was treated with various antihypertensive drugs, of which phenoxybenzamine (Dibenzyline) was the most effective. He was asymptomatic except for occasional headaches and excessive perspiration.

Physical examination revealed blood pressures of 170/110 in the supine position and 140/90 mm. Hg in the standing position. Funduscopic examination showed moderate arteriolar narrowing without hemorrhages or exudates. The heart was slightly enlarged and a grade-III systolic murmur was audible at the apex. Deep palpation of the abdomen revealed no masses and failed to alter the blood pressure. A urinary catecholamine determination was diagnostic of pheochromocytoma—880 μg. per day of free norepinephrine with no detectable epinephrine. An intravenous urogram was normal.

The major problem was thus to localize the tumor in this patient who had already undergone abdominal and thoracic explorations for pheochromocytoma. Since no significant amount of epinephrine was present in the urine, all possible sites had to be considered. The superior vena cava was catheterized by way of the right saphenous vein and blood samples were drawn as indicated in table 3. All the plasma values were elevated above normal. Only one plasma specimen showed a marked step-up in catecholamine concentration—the one obtained from high in the inferior vena cava in series 3. Since the patient's blood pressure was elevated rather uniformly during most of the procedure, the failure to demonstrate a consistent step-up in plasma catecholamine level in all of the high inferior vena caval samples was puzzling. Therefore the study was repeated 3 days later through the left saphenous vein. In only one of 3 trials was a marked step-up high in the inferior vena cava demonstrated. Thus, of 6 samples drawn from high in the inferior vena cava in 2 catheterizations only 2 showed a marked elevation in plasma catecholamine concentration above samples drawn from other sites. The findings were interpreted as being compatible with a pheochromocytoma in the upper abdomen. The failure to demonstrate a constant step-up high in the inferior vena cava was believed to be due to intermittent secre-

tion by the tumor or to poor sampling from a "streaming effect" in the inferior vena cava.

In October 1958 the patient underwent another abdominal exploration and a small tumor was finally located behind the inferior vena cava medial to the right adrenal gland. The excised tumor weighed 26 Gm. and contained 0.68 mg. per Gm. of norepinephrine and insignificant amounts of epinephrine.

The catheterization was of value in this case in localizing the tumor to the upper abdomen, thus permitting a fourth operation to be performed with some assurance that the proper area was being explored.

Case C

M. S., (case 17, table 1), a 63-year-old white woman, was admitted to George Washington University Hospital in July 1959 because of diabetes and hypertension of 2 years' duration and mental confusion during the previous week. The blood pressure varied from 260/155 to 160/100 mm. Hg and the patient was lethargic and confused. There was a diffuse macular rash over the trunk. The general physical examination was otherwise negative. The fasting blood glucose was 370 mg. per cent. An intravenous injection of 5 mg. of phentolamine (Regitine) produced a decrease in the blood pressure from 184/118 to 100/48 mm. Hg. A urinary catecholamine determination revealed 1,030 μg. per day of free norepinephrine and 510 μg. per day of epinephrine. An intravenous urogram was normal.

The high excretion of epinephrine suggested a tumor localized in one of the adrenal glands. Two series of blood samples were obtained along the vena cava by catheterization (table 3). Only 1 of the 2 samples drawn from high in the inferior vena cava, the level of the tumor, showed a marked step-up in plasma catecholamine concentration. In September 1958 a 47-Gm. pheochromocytoma was removed from the right adrenal region; the tumor contained 5.8 mg. per Gm. of norepinephrine and 2.4 mg. per Gm. of epinephrine.

Though the catheterization was an elective procedure in this case, the findings confirmed the presence of a tumor in one of the adrenal areas.

Case D

D. M., (case 7, table 1), a 28-year-old white man, was admitted to the National Heart Institute in May 1959 because of hypertension, excessive perspiration, tachycardia, and progressive loss of weight for 1 year. Two months prior to admission he had suffered an acute myocardial infarction. The patient was thin and perspired continuously. The blood pressure was 150/100 mm. Hg in the supine position and 90/70 mm. Hg in the standing position. The pulse rate ranged from 100 to 160 beats per minute. There was slight cardiac enlargement. Palpation of the abdomen revealed no masses, and massage of both flanks failed to alter the blood pressure consistently. The fasting blood glucose was 137 mg. per cent and the basal metabolic rate was +23 per cent. An intravenous urogram combined with laminography of the adrenal regions failed to reveal any abnormal masses. A 24-hour urine specimen contained 3,800 μg. of free norepinephrine but no detectable epinephrine.

The patient's activity was seriously limited by postural hypotension and tachycardia, occasional attacks of angina pectoris, and severe fatigue and anxiety. Blood samples were drawn during a single passage of a catheter down the venae cavae with duplicate specimens being obtained from high and low in the inferior vena cava (table 3). The catecholamine content of all the plasma samples was elevated, and a marked increase was found in the samples from high in the inferior vena cava. An attempt was made to lateralize the tumor by drawing samples during massage of each flank but no marked difference was found. The data were interpreted as demonstrating a tumor of the upper abdomen. At operation a pheochromocytoma was found in the right adrenal region. The excised tumor weighed 124 Gm. and contained 0.34 mg. per Gm. of norepinephrine but no detectable epinephrine.

In this case the catheterization provided unequivocal evidence of a tumor in the upper abdomen but gave no information concerning the involved side.

Case E

B. R., (case 10, table 1), a 33-year-old white woman (mother of C. R., case A) was admitted to the National Naval Medical Center, Bethesda, Maryland, in October 1958 because of hypertension. A sister, a niece, and a son all had documented pheochromocytomas. The blood pressure was 160/100 mm. Hg. The general physical examination was otherwise negative. The free catecholamine excretion on two separate occasions was 170 and 260 μg. per day of norepinephrine. After acid hydrolysis of the urine the value was 460 μg. per day of norepinephrine (normal after hydrolysis: 50 to 250 μg. per day). One year earlier the urinary catecholamines after acid hydrolysis had been 230 μg. per day of norepinephrine. No significant amount of epinephrine was found in any of the specimens.

The venae cavae were catheterized through the right saphenous vein (table 3). The samples drawn in series 1 were obtained during a single passage down the venae cavae with the patient at rest. Series 2 shows the values obtained after the intra-

venous injection of 0.025 mg. of histamine base. One minute after the injection the blood pressure fell from the control level of 160/100 to 100/50 mm Hg and the patient developed pounding headache and a facial flush. The blood pressure returned to control levels in 3 minutes. The sample from low in the superior vena cava was drawn 3 minutes after, and that from high in the inferior vena cava 5 minutes after the injection of histamine. Neither a prominent increase in blood pressure nor a rise in plasma catecholamine level occurred after the histamine injection. Ten minutes after the histamine test a third set of samples (series 3) was drawn across the adrenal area. The plasma catecholamine values showed a general downward trend during the procedure, and most of the values in series 2 and 3 were in the normal range. None of the specimens showed a step-up in catecholamine concentration convincing enough to suggest a tumor site. In July 1959 a 12-Gm. pheochromocytoma of the left adrenal gland was removed. The tumor contained 6.3 mg. per Gm. of norepinephrine but no significant amount of epinephrine.

In this case the blood pressure was sufficiently elevated during the catheterization to suggest that the tumor was secreting continuously. Nonetheless, the secretion rate was not high enough to produce a distinct increase in plasma catecholamine concentration in most of the blood samples drawn. In the presence of such a minimally secreting tumor and a negative histamine test, the catheterization was of no assistance in localizing the neoplasm.

Discussion

In the collected series of 79 cases of pheochromocytoma 78 per cent of all patients had tumors of the adrenal glands, and 95 per cent had tumors localized within the abdomen. These percentages are comparable to those reported previously by other authors.[1, 37] Thus, on a statistical basis alone, exploration of the abdomen through an upper transverse incision should provide a successful surgical approach in most cases of the disease.[38, 39] If a thoracic or cervical site can be excluded, nearly all pheochromocytomas should be accessible through this incision. A careful x-ray examination of the chest to exclude an extra-abdominal tumor is thus a very important procedure. Since both adrenal areas and the paraortic region must be examined in each case to rule out bilateral or multiple tumors,[37, 38] extensive efforts to localize abdominal chromaffin tumors preoperatively do not seem warranted in most patients with this disease. Deaths have occurred in patients with pheochromocytoma from procedures such as retroperitoneal gas insufflation and aortography.[40–42]

The differential assay of epinephrine and norepinephrine in the urine may be of value in suggesting an adrenal versus a nonadrenal tumor site. If the urine contains increased amounts of epinephrine as well as norepinephrine, the neoplasm is almost always in one of the adrenal areas. The 2 nonadrenal tumors of this type have been found in the organs of Zuckerkandl. No similar positive correlation exists, however, between a nonadrenal tumor site and a failure to produce epinephrine. If the increased excretion of catecholamines in the urine is limited to norepinephrine alone, the tumor may still be expected to lie in or near one of the adrenal glands in two thirds of the cases. In the remaining third in this group, however, the tumor will be extra-adrenal in location, and all possible sites must be considered.

The reason why epinephrine-producing tumors are localized almost entirely to the adrenal glands is not clear. Certain cells of the normal adrenal medulla have been shown to contain only norepinephrine, while others have the ability to N-methylate norepinephrine and thus form epinephrine.[43] The epinephrine-producing cells are therefore presumed to synthesize both amines. A histochemical study of one epinephrine-producing pheochromocytoma of the adrenal has been reported.[35] A few clusters of cells containing large amounts of norepinephrine were found among a background of cells containing small amounts of norepinephrine and considerable quantities of epinephrine; the authors were not convinced, however, that they had shown two distinct cell types comparable to those occurring in the normal adrenal medulla. It thus remains uncertain whether tumors that produce significant quantities of both amines are derived only from epinephrine-producing cells or whether they represent "mixed" tumors composed of both parent cell types. The

predominance of epinephrine-producing cells in the adrenal medulla probably accounts for the high incidence of epinephrine-producing tumors in this area. The almost negligible occurrence of epinephrine-producing pheochromocytomas elsewhere in the body remains unexplained, however, for epinephrine-produring cells are believed to be scattered throughout the course of the sympathetic chains and plexuses.[44] There is no evidence that nonadrenal epinephrine-producing chromaffin cells lack the capacity for tumor formation, as 2 tumors of these cells have been reported in the organs of Zuckerkandl. The infrequent occurrence of such tumors may reflect only a low incidence of epinephrine-producing cells relative to norepinephrine-producing ones in nonadrenal chromaffin tissue. If this is true, there is no fundamental biochemical or anatomic reason why an epinephrine-producing tumor cannot occur anywhere along the sympathetic system, and in the future such a case may be reported.

In certain unusual cases of pheochromocytoma accurate preoperative localization of the tumor may be necessary and catheterization of the venae cavae has proved useful in such instances. This procedure may be indicated (1) when previous surgical exploration has been negative (case B[45]), (2) when an extra-abdominal tumor is known to be present, which may or may not be the pheochromocytoma (case A), or (3) when the clinical situation of the patient is so desperate as to suggest that he may not survive a negative exploration (case E). It is indicated only when the tumor is a "pure" norepinephrine-producer and when the catecholamine secretion by the tumor appears to be continuous. Even in continuously secreting tumors, however, a consistent elevation of the plasma catecholamine level near the tumor site is not always found. This suggests that some of these tumors may be "paroxysmal" when considered on a minute-by-minute basis. Catheterization in our experience has been both a safe and accurate means of demonstrating the general level of the tumor in the body but not in lateralizing the neoplasm to one side or the other. However, using a spectrophotofluorimetric method of assay,[46] Vendsalu[47] found that "by careful sampling at various levels with the tip of the catheter directed against the walls of the vena cava, it was possible to localize and lateralize the tumor in three cases."

Finally, the relative value of plasma versus urinary catecholamine determination in the diagnosis of pheochromocytoma is well demonstrated by the values obtained in the 5 case reports. In patients A through D the plasma catecholamine concentration low in the inferior vena cava (representative of a peripheral venous sample) ranged from 12 to 23 μg. per liter. This is 2 to 4 times the upper limit of normal in our laboratory (6 μg./L.). In these same patients the free urinary catecholamines ranged from 800 to 3,800 μg. per day, an 8- to 38-fold increase over normal (<100 μg./day). In case E many of the plasma samples were clearly in the normal range, even though the patient was mildly hypertensive and had a catecholamine excretion at least twice normal. These findings illustrate that infusion rates of catecholamines sufficient to produce only modest elevations in plasma levels may result in large accumulations of these compounds in the urine over a period of time. Furthermore, while plasma catecholamine levels in patients with paroxysmal hypertension are increased only during the period of blood pressure elevation,[2, 48] the 24-hour urinary excretion in such cases is usually increased rather constantly.[1] For these reasons the determination of urinary catecholamines provides in most cases a more distinct and reproducible separation of normal persons from patients with pheochromocytoma than does the assay of plasma. More specific methods for the determination of plasma catecholamines than the one used in these studies are available.[46, 48, 49] These methods give normal values of less than 1 μg. per liter and may allow a clearer separation of normal from abnormal subjects than was found here. However, their application to a large number of patients in the diagnosis of pheochromocytoma has not been reported.

Summary

Data on urinary catecholamines in a collected series of 75 cases of pheochromocytoma, including 18 of our own cases, indicate that the differential assay of urinary norepinephrine and epinephrine may be of value in predicting the location of the tumor preoperatively. If there is a significant elevation of urinary epinephrine (42 per cent of all cases), the tumor may be expected to lie in or adjacent to one of the adrenal glands in about 95 per cent of cases. Other tumors of this type have been found only in the organs of Zuckerkandl. If the urine contains norepinephrine alone (58 per cent of all cases), the tumor will be found in one of the adrenal areas in about two thirds of the cases and in an extra-adrenal location in the remainder. In a few patients (6 per cent) of this type, the tumor may be extra-abdominal.

In some unusual cases more precise information on the location of the tumor must be obtained preoperatively. The demonstration of a marked step-up in plasma catecholamine concentration at the level of the tumor, the sampling being done by venous catheterization, is a useful and safe means of localizing the tumor. Five cases are presented illustrating the use of this procedure.

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Summario in Interlingua

Datos concernite con le catecholaminas urinari in un serie de 75 casos de pheochromocytoma—colligite ab varie reportos sed includente 18 casos de observation personal—indica que le essayo differential de norepinephrina e epinephrina urinari es possibilemente de valor in predicer le sito del tumor ante le operation. Si le epinephrina urinari es significativemente elevate (42 pro cento de omne le casos), on pote expectar que le tumor jace in un del glandulas adrenal o in adjacentia de illo. Iste expectation se provara correcte in 95 pro cento del casos. Altere tumores de iste typo ha essite trovate solmente in le organos de Zuckerkandl. Si le urina contine solmente norepinephrina (58 pro cento del casos), le tumor va esser trovate in un del areas adrenal in circa duo tertios del casos e in un area extra-adrenal in le remanente tertio. In alicunes inter iste patientes (6 pro cento), le tumor es extra-abdominal.

In certe casos inusual, plus precise informationes relative al sito del tumor debe esser obtenite ante le operation. Le demonstration de un marcate augmento del concentration de catecholamina in le plasma al nivello del tumor—determinate super le base de specimens obtenite per catheterismo venose—es un medio utile e salve pro localisar le tumor. Es presentate cinque casos que illustra le uso de iste procedimento.

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Neuroses of the Heart

Angina Pectoris

Etiology and Pathology: The following views have been entertained.

(1) That it is a neuralgia of the cardiac nerves. In the true form the agonizing cramp-like character of the pain, the suddenness of the onset, and the associated features, are unlike any neuralgic affection. The pain, however, is undoubtedly in the cardiac plexus and radiates to adjacent nerves. It is interesting to note in connection with the almost constant sclerosis of the coronary arteries in angina that Thoma has found marked sclerosis of the temporal artery in migraine and Dana has met with local thickening of the arteries in some cases of neuralgia. (2) Heberden believed that it was a cramp of the heart-muscle itself. This would explain the agonizing character of the pain and the suddenness of the onset as well as the frequency of the fatal termination; but if the cramps were general in the heart-muscle and similar to those which occur in the voluntary muscles, death would invariably ensue with great rapidity. Cramp of certain muscular territories would explain the attack. (3) That it is due to the extreme tension of the ventricular walls, in consequence of an acute dilatation associated, in the majority of cases, with affection of the coronary arteries. Traube, who supported this view, held that the agonizing pain resulted from the great stretching and tension of the nerves in the muscular substance. A modified form of this view is that there is a spasm of the coronary arteries with great increase of the intracardiac pressure.—WILLIAM OSLER, M.D. *The Prinicples and Practice of Medicine.* New York, D. Appleton & Company, 1893, p. 655.

Heart Block after Repair of Ventricular Septal Defect in Children

By RONALD M. LAUER, M.D., PATRICK A. ONGLEY, M.B.CH.B., JAMES W. DUSHANE, M.D., AND JOHN W. KIRKLIN, M.D.

THE CLOSE anatomic relationship of the conduction system of the heart to most ventricular septal defects[1-5] makes the occurrence of complete heart block a potential risk in the repair of these lesions. In our experience, when complete heart block has developed, it has often proved to be a serious complication. Although reversion to sinus rhythm occurs in the early postoperative period in many patients, others have persistent heart block; some of these die either in the immediate postoperative period or at some time after dismissal from the hospital. Of those who survive with complete heart block, some may be symptom-free but a few are troubled with frequent and potentially lethal Stokes-Adams attacks.

The purpose of this paper is to review an experience with complete heart block following the repair of ventricular septal defect and ventricular septal defect associated with infundibular or valvular pulmonic stenosis or with both in the pediatric age group. The data concerning adult patients are not analyzed as yet. We will mention certain changes in surgical technic which seem to have affected the incidence of heart block and will discuss briefly immediate and long-term therapy.

Material and Methods

From March 1955 to April 1959, 174 patients with ventricular septal defect and 124 patients with ventricular septal defect associated with infundibular or valvular pulmonary stenosis were referred from the Section of Pediatrics for open intracardiac repair. The group of patients designated as "having ventricular septal defect" includes those with isolated ventricular septal defect and those with ventricular septal defect associated with various intracardiac or extracardiac lesions other than pulmonic stenosis. Patients with ventricular septal defect as part of a common atrioventricular canal have been excluded from this study as also have patients with ventricular septal defect associated with corrected transposition of the great vessels. The group of patients described as having ventricular septal defect associated with infundibular or valvular pulmonic stenosis includes those with tetralogy of Fallot as well as those with ventricular septal defect in whom the pulmonic stenosis and the arrangement of the great vessels are not those usually recognized as typical for tetralogy of Fallot.

Included in this study were 94 male and 80 female patients with ventricular septal defect. Their ages ranged from 2½ months to 15 years. Seventy-nine boys and 45 girls had ventricular septal defects associated with infundibular or valvular pulmonic stenosis or with both. Their ages ranged from 6 months to 15 years.

Three types of surgical technics were employed for the 298 patients included in this study: 1. From March 1955 to July 1956, open intracardiac repair was carried out on the beating heart. 2. From July 1956 to the present, induced asystole has been a standard part of the procedure. During the period from July 1956 to April 1958, ventricular septal defects were closed either by the placement of a prosthetic sponge or by direct suture. 3. In April 1958, the method of repair of the ventricular septal defect was altered by the introduction of a direct suturing technic designed specifically to avoid the conduction system.

The surgical details of perfusion,[6, 7] the methods of repair of infundibular and valvular pulmonic stenosis,[8] and of ventricular septal defect prior to the introduction of the present suturing technic[9] have been described previously. The present suturing technic is to be described in a subsequent communication. An artificial pacemaker[10] was available to all patients in the series, in early cases with an external electrode and in later cases with an internal electrode.[11]

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The records of the 298 patients have been reviewed with reference to incidence and to some factors affecting the occurrence of postoperative complete heart block. Data concerning the frequency of reversion to sinus rhythm, and death or survival following the development of complete heart block have been obtained.

Intracardiac pressure was measured either by cardiac catheterization prior to operation or by direct needle puncture at the time of operation.

Remarks concerning symptoms are based on examination while in the hospital or at follow-up visits, and from letters received from the parents or referring physicians since dismissal from our care.

Over-all incidence of complete heart block may not be so important a consideration as the incidence of permanent heart block, that is, heart block present at death or dismissal. Permanent heart block is more likely related to sutures, while temporary heart block may be related to administration of digitalis, sequelae of cardiac anoxia, or to other temporary causes. Therefore, the incidence of block persisting until the time of death or dismissal will be stressed, for temporary heart block is rarely a serious problem when properly treated.

Results

The data in tables 1 and 2 indicate no difference in the over-all incidence of complete heart block at death or dismissal from the hospital between the patients operated on for ventricular septal defect and those operated on for ventricular septal defect associated with infundibular or pulmonic stenosis, as the incidence was approximately 10 per cent of each group. These tables also relate the incidence of complete heart block at death or dismissal to each of the 3 surgical technics previously mentioned. With the introduction of asystole, this incidence increased in patients with ventricular septal defect (table 1), but more recently with use of the present suture method it has fallen to 5 per cent, nearly as low an incidence as that obtained after operations on the beating heart. Among patients with ventricular septal defect and infundibular or pulmonic stenosis the incidence of complete heart block at death or dismissal changed very little when asystole was introduced, but has diminished with utilization of the present technic (table 2).

No relationship was demonstrated between the incidence of heart block and age. The ages of patients who had complete heart block ranged from 7 months to 11 years. There were 30 boys and 18 girls. In those cases of ventricular septal defect and complete heart block in which postoperative intracardiac pressures were available, right ventricular pressures showed an appreciable fall in most instances (fig. 1).

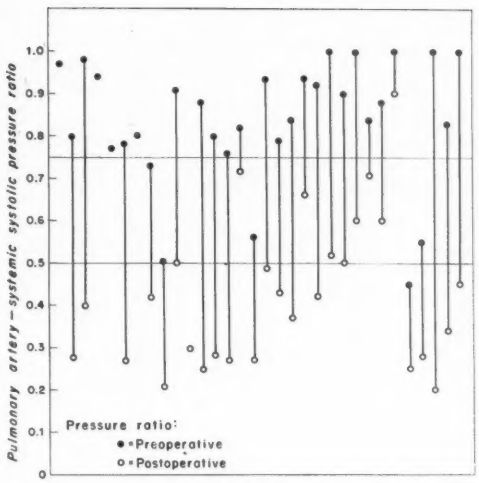

Figure 1

Ratios of pulmonary artery pressure to systemic systolic pressure before and after operation for ventricular septal defect on 32 patients in whom complete heart block developed.

The relationship between the incidence of postoperative complete heart block and the ratio of preoperative pulmonary artery pressure to systemic systolic pressure is shown in figure 2 for 158 patients with ventricular septal defect for whom data concerning pressures were available. The over-all incidence of postoperative complete heart block was 3 per cent among patients with ratios of less than 0.50, 10 per cent among those with ratios from 0.50 to 0.74, and 30 per cent among those with ratios of 0.75 or more. The incidence of permanent heart block was, of course, lower than this incidence, being for example 21 per cent among the total cases with ratios of 0.75 or more. It can be seen that the over-all incidence of complete heart block was the highest in those patients with severe pulmonary hypertension.[12]

Table 1

Ventricular Septal Defect

	Total patients operated on	Complete heart block at some time							
		Total		Reverted to sinus rhythm		Continued to death or dismissal from hospital			
						Died in hospital	Survived*	Total	
		No.	%	No.	%			No.	%
Before asystole: March 1955—July 1956	38	4	11	3	8	1	0	1	3
Asystole: July 1956—April 1958	81	20	25	5	6	7	8	15	19
Asystole and new suture technic: April 1958—April 1959	55	9	16	6	11	2	1	3	5
Total	174	33	19	14	8	10	9	19	11

*Patients who were dismissed from the hospital with complete heart block. The patients who died subsequent to dismissal are included in this group.

Table 2

Ventricular Septal Defect Associated with Infundibular or Ventricular Pulmonic Stenosis or Both

	Total patients operated on	Complete heart block developed							
		Total		Reverted to sinus rhythm		Continued to death or dismissal from hospital			
						Died in hospital	Survived*	Total	
		No.	%	No.	%			No.	%
Before asystole: March 1955—July 1956	20	3	15	1	5	2	0	2	10
Asystole: July 1956—April 1958	50	7	14	1	2	3	3	6	12
Asystole and new suture technic: April 1958—April 1959	54	5	9	2	4	3	0	3	6
Total	124	15	12	4	3	8	3	11	9

*Patients who were dismissed from the hospital with complete heart block. Patients who died subsequent to dismissal are also included in this group.

In the group of patients in whom data on pressure were available, 60 per cent had ratios of pulmonary artery to systemic systolic pressure of 0.75 or more in the period before asystole, 49 per cent in the period of asystole with the original suture technic, and 56 per cent in the most recent period with the present suture technic. Thus the fall in the incidence of permanent complete heart block with the introduction of the new suture technic cannot be attributed to the fact that more patients selected for operation in the most recent period have had low pressure ratios.

The fate of the 33 patients with ventricular septal defect who had complete heart block at any time is shown in table 1. In 14 of these

(43 per cent) normal sinus rhythm returned; 10 (30 per cent) died with complete heart block, and 9 (27 per cent) were dismissed from the hospital with complete heart block. Complete heart block developed in 15 of the 123 patients operated on for ventricular septal defect associated with pulmonic stenosis (table 2). In 4 of these (27 per cent) normal sinus rhythm was resumed; 8 (53 per cent) died with complete heart block, and 3 (20 per cent) were dismissed from the hospital with complete heart block.

The time of reversion to normal sinus rhythm is shown in figure 3. This occurred on the second to sixteenth postoperative day in 14 patients with ventricular septal defect, and from the second to the twentieth postoperative day in 4 patients with ventricular septal defect and pulmonic stenosis.

The mode of death, which was apparently a direct result of complete heart block, was sudden cardiac asystole refractory to the electric pacemaker. The day of death in those patients with complete heart block who succumbed during the immediate postoperative period is shown in figure 4. Most deaths occurred in the immediate postoperative period. In some patients who died with complete heart block, bradycardia or asystole did not seem to be the sole determining factors resulting in death. Three who died in the immediate postoperative period had respiratory complications and two late deaths occurred, one following a febrile illness, and one following a second operation.

Heart block developed in the operating room in 37 patients, within a few hours of the completion of the operation in 4 and on the first postoperative day in 4. The latest development of heart block was on the eighth postoperative day. Since in the great majority of our patients the heart block developed at the time of operation, we do not have enough cases of delayed block to allow statistical analysis; so far, however, there is no obvious difference in the survival rates or in the percentage of those with reversion to normal sinus rhythm in the two groups.

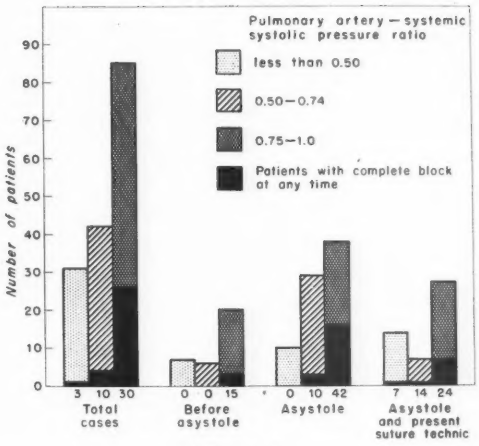

Figure 2

Ratios of pulmonary artery pressure to systemic systolic pressure before operation for ventricular septal defect on 158 patients. Data were not available for the other 16 patients in this group. Per cent of patients in each ratio group who had complete block at any time, which in some instances was temporary, is indicated by number beneath column.

Course after Dismissal

Twelve patients (cases 1 to 12, fig. 5) in this study were dismissed from the hospital with complete heart block. Three of these died subsequently. The first death was that of a girl (case 12, fig. 5) with ventricular septal defect repaired at the age of 5 years in 1957. Complete heart block developed in the operating room. In the early postoperative period frequent Stokes-Adams attacks occurred. On the twenty-fourth postoperative day sinus rhythm developed but continued to alternate with 2:1 heart block until she left the hospital. The postoperative course was otherwise uneventful, and she was discharged from the hospital without symptoms. On the fifty-fifth postoperative day death occurred suddenly at home.

In the second patient (case 6, fig. 5) a 6-year-old boy with ventricular septal defect and mild infundibular pulmonic stenosis repaired in 1957, complete heart block developed in the operating room. Frequent Stokes-Adams attacks occurred in the hospital after opera-

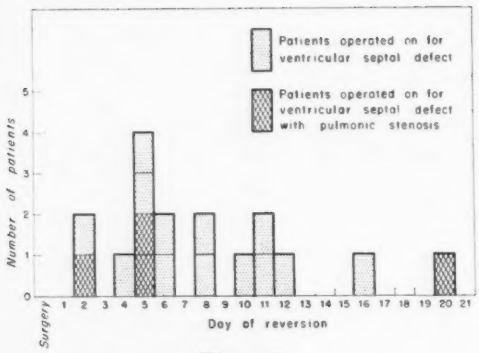
Patients operated on for ventricular septal defect
Patients operated on for ventricular septal defect with pulmonic stenosis
Number of patients
0
1
2
3
4
5
Surgery
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Day of reversion

Figure 3

Postoperative day of reversion to sinus rhythm in 17 patients. Day of reversion was not recorded for 1 patient.

tion and occasionally after dismissal. About 1½ years after operation a febrile illness developed and death occurred suddenly.

The third patient (case 11, fig. 5) was a girl, 6 years old in early 1958, when a repair of tetralogy of Fallot was made by the use of a prosthesis in the ventricular septal defect and plastic reconstruction of the right ventricular outflow tract and pulmonary artery. Complete heart block occurred in the operating room. However, she had no symptoms of bradycardia, either in the hospital or after dismissal. In the early postoperative period a systolic murmur, which was thought to be the result of an incomplete repair of the ventricular septal defect, was noted at the lower left sternal border. After dismissal the murmur became progressively louder and roentgenograms of the thorax showed progressive dilatation of the pulmonary artery in the region of the prosthesis. Ten months after the first procedure an aneurysm in the region of the reconstructed outflow tract was repaired and the ventricular septal defect was repaired again. The patient died shortly after this operation.

Three patients among the 9 surviving with complete heart block have had symptoms of heart block since they left the hospital. One (case 4, fig. 5) was a boy aged 2 years in 1957 when he was operated on for ventricular septal defect. Heart block developed in the operating room. Both in the early postoperative period and after discharge frequent Stokes-Adams attacks occurred. Because of the frequency of these spells it was necessary to readmit him for observation and adjustment of therapy. For the last 14 months he has had no Stokes-Adams attacks, but still complains of headache or chest pain when his pulse rate becomes slower than 30 per minute. He is given isoproterenol (Isuprel) hydrochloride daily.

In the second patient, a girl (case 5, fig. 5), whose ventricular septal defect was repaired at the age of 2 years in 1957, complete heart block also occurred in the operating room. In the postoperative period the rhythm varied from normal sinus to complete heart block, often changing abruptly from the one to the other. When the rhythm changed from normal sinus to heart block, Stokes-Adams attacks would occur, requiring the use of the electric pacemaker. The child was readmitted to the hospital 2 months after dismissal because of frequent spells. She was digitalized and has since remained in complete heart block. Following her second discharge, Stokes-Adams attacks continued for about 2 weeks and then ceased. For the past 15 months, her pulse rate has been around 50 per minute and she appears to be in good health.

The ventricular septal defect of the third surviving patient (case 1, fig. 5) who has had symptoms after dismissal was repaired at the age of 3 years in 1957. Two Stokes-Adams attacks occurred during postoperative hospitalization, and another during the first month after dismissal. For the first 6 months following operation congestive heart failure persisted. Since then he has been without symptoms, fully active, with a pulse rate of about 40 beats per minute.

The remaining 6 patients (cases 2, 3, 7 to 10, fig. 5) who survive with complete heart block have no symptoms from bradycardia and no periods of asystole.

Surgical Technics and Discussion

During the period when ventricular septal defects were repaired while the heart was

beating, the incidence of complete heart block present at death or dismissal was low. This is attributed to the fact that the beating heart allowed observation of the effect of each suture on ventricular rhythm. If block occurred, the offending suture was removed and replaced so that conduction would not be permanently affected. In some instances, however, the complete heart block persisted many days even when the stitch had been immediately removed. Although the introduction of induced asystole allowed a higher incidence of accurate closure of the defects, the incidence of permanent heart block increased from 3 to 19 per cent among patients operated on for ventricular septal defect. Others[14] have had similar experiences. Although not all would agree, it is our belief that this increase was due to interference with the conduction bundle which passed unnoticed with the heart at rest. Paradoxically, the increase in incidence of heart block on changing from the beating heart technic to asystole was not seen in the patients operated on for ventricular septal defect associated with pulmonic stenosis.

In order to minimize the occurrence of postoperative permanent heart block and to continue using asystole because of the more accurate repair obtainable, the present suture technic was evolved specifically to avoid the conduction system. Since adoption of this technic, the incidence of permanent heart block at death or dismissal has fallen from 19 to 5 per cent in patients with ventricular septal defect; and from 12 to 6 per cent in patients with ventricular septal defect and infundibular or pulmonary valvular stenosis. It is apparent that none of the technics utilized has eliminated the occurrence of permanent heart block. This is not surprising, in view of the probable anatomic variations in distribution of the conduction system and human frailties in application of surgical technics. Also unforeseen complications, such as spread of hemorrhage from a suture site into conduction tissue,[15] are always possible. Yet a low incidence (5 to 6 per cent) of permanent heart block, present at death or dismissal, has been attained.

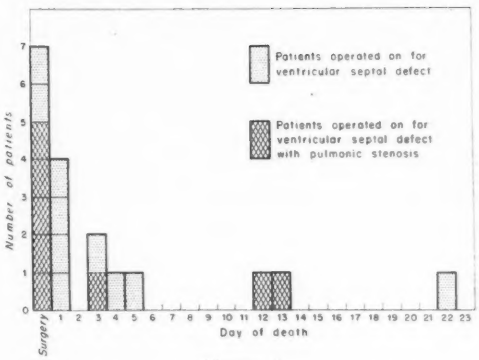
Patients operated on for ventricular septal defect
Patients operated on for ventricular septal defect with pulmonic stenosis
Number of patients
Surgery
Day of death

Figure 4

Postoperative day of death of 18 patients with complete heart block.

Treatment of Complete Heart Block

Early Postoperative Period

Unlike congenital heart block,[16–19] which is frequently asymptomatic, heart block resulting suddenly from the surgical repair of a ventricular septal defect may cause serious symptoms. These vary in severity from a feeling of discomfort and restlessness to Stokes-Adams attacks characterized by unconsciousness, seizures, and occasionally sudden death. Likewise it appears likely that in the postoperative patient, cardiac output and coronary blood flow may be adversely affected by a very slow heart rate, possibly with fatal sequelae.

During the 4-year period covered by this study, several items have been altered in the immediate postoperative care of patients. Thus it is not possible to establish what is the optimal treatment from a review of the methods used. Certain points that seemed important have been incorporated into a routine of treatment that appears rational and is usually effective.

When complete heart block persists for more than a few minutes after the heart is restarted in the operating room, a wire electrode is imbedded into the right ventricle over the outflow tract and an external electrode is inserted into the skin of the chest wall.[11] The electrode wires are connected to an appropriate electric pacemaker. The units

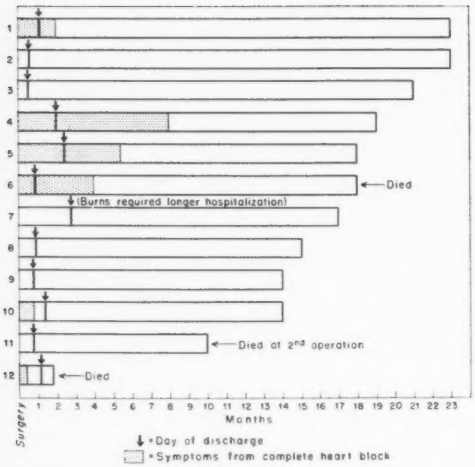

Figure 5

Course to May 1959 of 12 patients who had complete heart block at time of dismissal from the hospital.

supplied by the Electrodyne Co., Norwood, Massachusetts, and by Medtronic, Inc., Minneapolis, Minnesota, have been used with satisfaction. The heart rate is adjusted to a level approximating that seen postoperatively in patients of the same age as the child being treated. The amplitude of the stimulus is adjusted until an adequate response occurs with each electric impulse.

When complete heart block first occurs in the postoperative period, external electrodes applied to the chest wall are used, or an internal myocardial wire is placed percutaneously[20] and used as just described.

A patient whose heart is being driven by a pacemaker or has been driven by a pacemaker recently is watched continuously for a number of days by special nurses who also watch an oscillographic electrocardiographic monitor. If the heart is not responding to the pacemaker, the amplitude of the stimulus is increased until an adequate cardiac response occurs. A patient whose heart is no longer under pacemaker control is put back immediately on it by the nurse if an indication arises.

The heart is driven by the electric pacemaker continuously for 72 hours after operation unless the electrocardiograms show that the heart is in sinus rhythm. When reversion to sinus rhythm is suspected, the rate of the pacemaker is cautiously diminished to observe the rhythm of the patient's heart. If there is sinus rhythm, use of the electric pacemaker is discontinued, but the electrodes are left in place so that the pacemaker can be made to function immediately if heart block again develops. Isoproterenol is not administered while the patient's heart is being driven by the pacemaker.

When the heart has been driven by the electric pacemaker for 3 to 4 days, and the block is still present, the pacemaker rate is cautiously reduced to see whether the heart itself can maintain an adequate idioventricular rate. If the rate is adequate, the electrodes are left in place and the patient is observed closely for signs of bradycardia, systemic hypotension, and inadequate cardiac output. It is important that the patient never be left alone during this period.

If the heart rate is inadequate to maintain the patient when the electric pacemaker is stopped, it is turned on immediately and used for another 24 hours. On the following day the patient is given isoproterenol by rectum about a half an hour before the rate of the pacemaker is decreased again. This procedure is repeated daily until the heart rate stabilizes at an adequate rate.

For the patients who continue in complete heart block after the pacemaker is stopped, isoproterenol is administered by rectum every 2 to 6 hours if necessary to maintain a stable and adequate ventricular rate. In some children 40 to 50 beats per minute is an adequate rate, while others are uncomfortable unless the rate is somewhat faster. A slow heart rate is better tolerated 10 to 14 days after operation than it is 4 to 5 days after it.

Isoproterenol hydrochloride is supplied in 10 and 15 mg. tablets for sublingual use. We have given these tablets by rectum to children in the following dosage: 2.5 mg. for infants and small children, 5 to 15 mg. for larger children. Prior to insertion into the rectum the nurse checks the time of the last bowel

movement. If there has been no recent evacuation, the child is given a glycerine suppository to cause evacuation of the rectum before the medication is administered.

Long-Term Treatment

Patients who still have complete heart block at dismissal but do not have symptoms or unfavorable signs related to it are not maintained on special treatment. For those patients with symptoms treatment has been a matter of trial of various drugs that have the properties of increasing the rate and maintaining the stability of idioventricular rhythm, namely isoproterenol and ephedrine. We have also tried atropine by parenteral administration in several patients with disappointing results. The use of digitalis is apparently not contraindicated under these circumstances and has seemed to be beneficial at times.

For patients in whom the bradycardia and asystoles recur in a pattern, isoproterenol is administered about half an hour prior to the time of expected trouble. Oral administration of the drug is effective for some children, although for others rectal administration is better.

It is important to stress the value of careful, patient management of these children. Although the threat of sudden death may always be present, some children with serious symptoms in the early months after operation eventually stabilize and become well adjusted to a slow ventricular rate.

Summary

From March 1955 to April 1959, 174 patients with ventricular septal defect and 124 patients with ventricular septal defect associated with pulmonic stenosis were referred from the Section of Pediatrics of the Mayo Clinic for open intracardiac repair.

Forty-eight of these 298 patients had complete heart block at some time following operation. Eighteen of the patients with heart block died in the immediate postoperative period, 18 had reversion to normal sinus rhythm, and 12 were discharged from the hospital with complete heart block. Three of these 12 patients died subsequently. Two died presumably as a direct result of complete heart block and a third died following a second open cardiac operation. Of the 9 surviving patients, 3 have had serious bradycardia or periods of asystole and 6 have no symptoms from heart block.

One of 3 surgical technics was employed for all the patients in this study with variation in incidence of block with the use of each technic. Other factors that might relate to the incidence of heart block are discussed.

The management of the patient with complete heart block both in the immediate postoperative period and after dismissal from the hospital is described.

Addendum

From April 1959 to April 1960, 90 children with ventricular septal defect and 75 with tetralogy of Fallot were operated on. The suture technic was the same as that used from April 1958 to April 1959.

Of the 90 children with ventricular septal defect, 6 (7 per cent) had complete heart block at some time during the postoperative period, and normal sinus rhythm returned to 5 of these while they were still in the hospital, leaving only 1 patient (1 per cent) with complete block at death or dismissal. Of the 75 patients with ventricular septal defects and pulmonic stenosis, 10 (13 per cent) had heart block at some time during the postoperative period and 6 (8 per cent) were still in block at death or dismissal.

In addition to the 3 patients who died in block following dismissal, reported in the main paper, one other died at Christmastime, 1959, while sitting at the dinner table. This means that 4 of the 12 patients originally discharged in block have now died.

Summario in Interlingua

Inter martio 1955 e April 1959, 174 patientes con defectos ventriculo-septal e 124 patientes con defectos ventriculo-septal in association con stenosis pulmonic esseva destinate per le Section de Pediatria del Clinica Mayo al reparo per un aperte operation intracardiac.

Quaranta-octo de iste 298 patientes experientiava un complete bloco cardiac a un tempore o un altere post le operation. Dece-octo del patientes con bloco cardiac moriva immediatemente post le operation; 18 reverteva a normal rhythmos sinusal; e 12 esseva dimittite ab le hospital con complete bloco cardiac. Tres de iste 12 moriva subsequentemente. Duo moriva presumitemente como resultato directe del complete bloco cardiac, e un tertie moriva post un secunde aperte operation cardiac. Inter le 9 patientes vivente, 3 ha manifestate serie formas de bradycardia o periodos de asystole, e 6 ha monstrate nulle symptomas attribuibile al bloco cardiac.

Un de 3 differente technicas chirurgic esseva empleate pro omne le patientes in iste studio. Le incidentia de bloco cardiac differeva secundo le technica usate. Altere factores que es possibilemente relationate al incidentia de bloco cardiac es discutite.

Es describite le programma de tractamento pro patientes con complete bloco cardiac, tanto durante le periodo immediatemente post le operation como etiam al tempore subsequente al dimission ab le hospital.

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Vasoconstriction and Medial Hypertrophy in Pulmonary Hypertension

By C. A. WAGENVOORT, M.D.

THAT increased thickness of the medial layer of the muscular pulmonary arteries is an almost constant feature of pulmonary hypertension has been well established. Usually it is referred to as medial hypertrophy. This increase, however, is not necessarily an expression of hypertrophy, since it may result from vasoconstriction without any real increase of muscular tissue in the wall of the vessel.

In order to clarify this point the medial thickening of pulmonary arteries in cases of congenital cardiac disease with pulmonary hypertension was studied. Attention also was paid to differences in various parts of the same lung in cases of pulmonary hypertension and in normal persons.

Materials and Methods

One or both lungs in 10 cases without any evidence of cardiac or pulmonary disease were used as controls. These lungs were selected in so far as possible from patients in the same age group as the patients with pulmonary hypertension. The ages of these patients ranged from 6 weeks to 39 years. In addition one, sometimes both, lungs of 17 patients with pulmonary hypertension were studied. Ten of these patients had ventricular septal defects, 1 ostium atrio ventriculare commune, 5 atrial septal defects, and 1 had patent ductus arteriosus with coarctation of the aorta. All patients died after cardiac operation. Only cases in which the pressure in the pulmonary artery or right ventricle had been measured during cardiac catheterization were included. The cases of pulmonary hypertension were divided into 2 groups according to the level of pulmonary arterial systolic pressure. A pressure of 80 mm. Hg systolic was arbitrarily chosen as the lower limit of the high pressure group. All lower pressures were included in the moderate pressure group. The youngest patient was 2 years old, the oldest 47.

One of the lungs, usually the right one, if not damaged at necropsy, was perfused via the pulmonary artery first with 4 per cent solution of formalin and then with barium sulfate-gelatin mixture at the systolic pressure recorded during life by cardiac catheterization. For normal lungs a pressure of 15 to 20 mm. Hg was used. The other lung was kept as a control if not needed for other purposes. Arteriograms were made of the whole perfused lung and of its segments after segmental dissection.[1] In perfused lungs the number of vessels suitable for measurement was greater than in nonperfused lungs, in which the vessels are often more or less collapsed. Ten blocks of tissue were taken from 5 different segments of each lung, namely from the apical and pectoral segments of the upper lobe, the lateral segment of the middle lobe or the lingula, and the apical and the anterobasal segments of the lower lobe. One block was taken at the periphery and another nearer the hilum. Sections were cut 6 μ thick and stained with hematoxylin and by Weigert's method for elastin, counterstained with van Gieson's stain.

The method to be employed required careful consideration. It seemed necessary for our purpose to determine the thickness on cross section of the media of a great number of pulmonary arteries and to measure the diameter of these arteries in both control lungs and in lungs affected by pulmonary hypertension. Such measurements, however, give no reliable information about a possible increase in muscular tissue within the vessel wall. If the results so obtained in lungs with pulmonary hypertension differ from those in controls, it is not possible to state that a thicker-walled vessel has more muscle than a vessel with corresponding medial thickness in a control case or that the vessel is thicker because of spasm. Therefore further data were needed in order to give a quantitative expression of the amount of medial tissue present. It would have been possible to calculate the mean surface area of the muscular layer of a great number of vessels chosen at random in hypertensive lungs and to compare the results with the mean surface area of the muscular layer in arteries in normal lungs. This approach presupposes that the vessels under these different conditions are more or less comparable. There is, however, reason to believe that they are not comparable. It has been pointed out by Heath and Whitaker[2] and Heath and Best[3] that in pulmonary hypertension the number of the smallest arterial vessels increases, since many at the arteriole level, normally without a distinct media, possess a muscular coat. An increase in the number of small muscular arteries, however, will lead to a decrease

From the Pathological Laboratory, State University, Leyden, Holland.

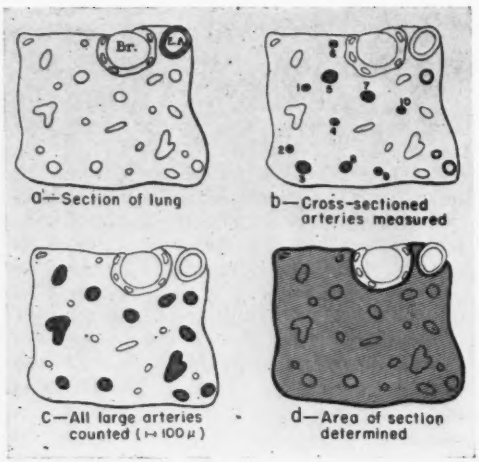

Figure 1

Diagrammatic description of method employed. a. *Scheme of section of lung with muscular pulmonmonary arteries indicated (Br. = bronchus; E.A. = elastic artery).* b. *At least 10 arteries cut in true cross section were measured in each section; these were at random. The relative medial thickness and the index of medial cross-sectional area were calculated and tabulated according to external diameter of the vessel (less than 100 μ or 100 μ or more). In this way the ratio between the 2 classes of arteries was obtained.* c. *All large arteries (100 μ or more in diameter) in the section were counted irrespective of their plane of section.* d. *The surface area of the section, exclusive of large bronchi and vessels, is determined and the number of large muscular arteries per square centimeter is calculated. The ratio between large and small arteries being known, the number of the latter can be calculated. The mean area of the media of the arteries in true cross section can be used to determine the index of the area of the media on cross section per square centimeter of pulmonary tissue.*

of the mean cross-sectional area of media. This effect to a certain degree may mask real hypertrophy of the media.

A more appropriate method, therefore, is to establish the amount of arterial muscular tissue per unit of lung tissue, and this method was employed.

Selection of Arteries

The following procedures were carried out: For our measurements only muscular arteries that were virtually circular on cross section and that had a definite muscular media, indicated by internal and external elastic membranes, were included. As transitions are found between large muscular arteries and elastic arteries in which only a limited number of elastic membranes are present, all transitional forms were excluded from study. The arteries were taken entirely at random, whenever a vessel, meeting the conditions stipulated, presented itself in the field of view. Although they were not selected for size, they were classified into 2 groups: arteries less than 100 μ in diameter and those 100 μ or more in diameter. In this way the frequency of large and small arteries was ascertained.

Measurements Made

The diameter (d) of the vessel, exclusive of the adventitia, was measured and the thickness of the media (m) between the outer and inner elastic layer was measured also. At least 10 muscular arteries in each block of tissue, that is, at least 100 arteries were measured per lung, except in case 12 (fig. 1) in which not more than 88 pulmonary arterial branches could be found in the 10 sections studied. More than 100 vessels, indeed as many as 196 vessels, were measured in some cases in which great dimensional variations were apparent. From the measurements obtained, the thickness of the media was expressed as a percentage of the diameter.

Calculation of Area of Media on Cross Section

The cross-sectional area of the media (c), which gives a better indication for the presence of hypertrophy,[4] was deduced from the data already obtained according to the formula $c = (dm - m^2)\pi$. In this way the mean area of the medial surface could be established both for small and larger arteries in each case. For the sake of convenience the area of the medial surface was always expressed as an index of the cross-sectional area and the results of this calculation, therefore, were not multiplied by π.

Determination of Mean Cross-Sectional Area of Media per Unit of Lung Tissue

This was done by obtaining the mean cross-sectional area of the media of both the large and the small muscular arteries. This in turn was multiplied by the number of vessels per square centimeter of lung section. Since the measured vessels were relatively scarce per surface area of lung because of their having been selected for circular cross section, it was judged better not to confine ourselves to these for counting numbers. Since the small vessels can be counted only under high-power magnification, screening a big area in this way is a laborious and unpractical procedure.

For that reason only muscular arteries of 100 μ or more in diameter were counted in all the sections previously used for measuring the vessels. If 2 successive countings yielded different results, the mean of these was taken. Ramifying arteries

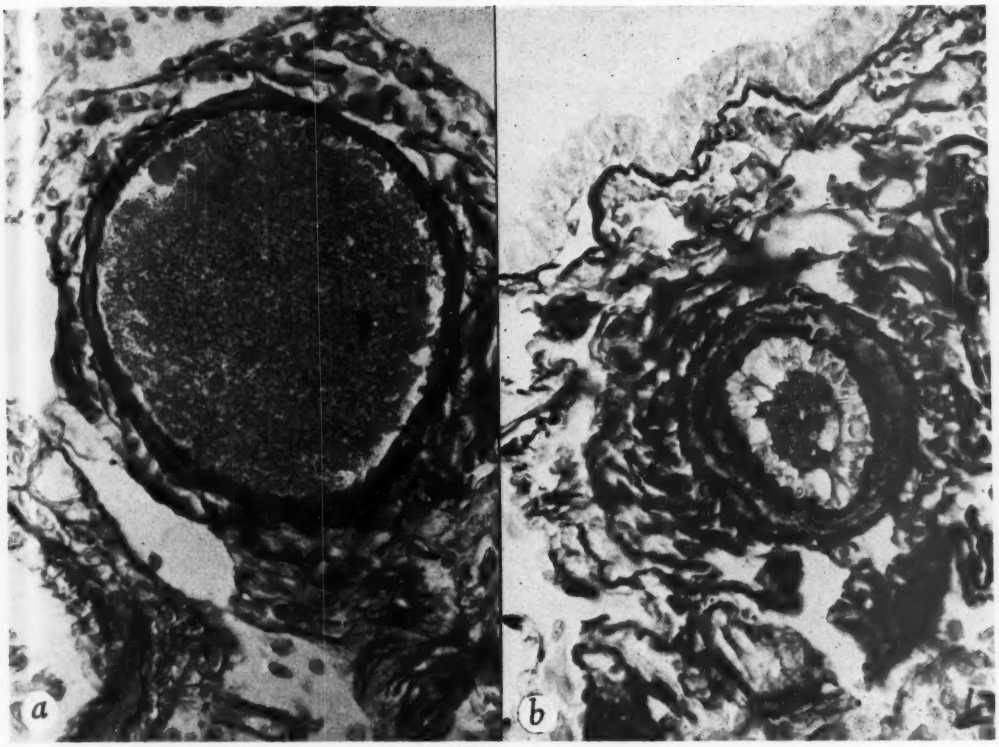

Figure 2

a. *Normal pulmonary artery (case 3, fig. 1) filled with injection mass. The medial thickness is about 3 per cent of the diameter. (Weigert's stain for elastin, counterstained with van Gieson's stain; × 350.)* b. *Normal pulmonary artery (case 8, fig. 1) filled partly with blood and partly with injection mass. There is a marked thickening of the media (the ratio of the media to the diameter is about 16 per cent). This probably resulted from vasoconstriction. (Weigert's and van Gieson's stains; × 350.)*

were counted as 1 vessel when they were connected in the section by a distinct common adventitia.

Then the surface area of all sections was measured with a planimeter, and the surface area of great bronchi or vessels, which could disturb the result, was deducted. Then the number of arteries measuring 100 μ or more was calculated per square centimeter of lung parenchyma. The ratio between vessels measuring less than 100 μ in diameter and those measuring 100 μ or more being known, the approximate number of the former could be calculated, and with the use of the mean cross-sectional area the total cross-sectional area of the media of arteries in both categories could be found. Their sum indicates an index of the amount of vascular muscle tissue per square centimeter of lung parenchyma. In figure 1 the method employed in determining the mean cross-sectional area of the media per square centimeter of tissue is illustrated.

Results

It seemed important to establish whether perfusion of the lungs with formalin and barium sulfate had an appreciable effect on the relative thickness of the media. When the left lung was not injected and could be used as a control, our measurements in both the normal and hypertensive groups showed a constant but slight difference in medial thickness, and the arteries that were not injected were somewhat more thick-walled than those that were injected. This decrease in the mean ratio of media to diameter of the vessel $\left(\frac{m}{d}\right)$,

Table 1

Mean Medial Thickness, Standard Deviation, and Skewness of Frequency Curve of Pulmonary Arteries in Controls and in Moderate and Severe Pulmonary Hypertension

	Patients	Arteries studied	Medial thickness		Skewness
			Mean	S.D.*	Mean
Controls	10	1539	4.64	1.08	1.85
Pulmonary hypertension					
Moderate pressure	6	809	7.61	1.98	1.02
High pressure	11	1982	11.88	1.94	0.61
Significance of differences according to pressure					
Normal to moderate pressure			$T = 2.44$ $P = 0.0156$	$T = 2.01$ $P = 0.0444$	$T = 1.90$ $P = 0.0574$
Normal to high pressure			$T = 3.84$ $P < 0.001$	$T = 3.27$ $P = 0.0014$	$T = 3.27$ $P = 0.0014$
Moderate pressure to high pressure			$T = 2.30$ $P = 0.0214$	$T = 1.66$ $P = 0.0970$	$T = 1.74$ $P = 0.0818$

*Standard deviation.

Table 2

Mean Medial Thickness in Various Zones of the Lung in Controls and in Groups with Moderate and High Pulmonary Hypertension

	Controls		Pulmonary hypertension			
			Moderate pressure		High pressure	
	Arteries measured	Media, per cent of diameter	Arteries measured	Media, per cent of diameter	Arteries measured	Media, per cent of diameter
Zone of lung						
Upper*	624	4.3	322	7.6	776	12.2
Middle†	612	4.4	321	7.4	818	11.4
Lower‡	303	4.2	166	7.9	388	11.1
Blocks of lung						
Proximal	759	4.3	410	7.7	1006	11.9
Peripheral	780	4.3	399	7.5	976	11.4

*Measurements from apex and pectoral segments of upper lobe.

†Measurements from lateral portion of middle lobe, or lingula, and apex of lower lobe.

‡Measurements from anterobasal portion of lower lobe.

as a result of perfusion, was always less than 20 per cent and averaged no more than 7.8 per cent. Perfusion under controlled pressure, therefore, apparently has only a minor effect on the thickness of the arterial wall.

Controls

In comparison to the arteries of the greater circulation the pulmonary vessels are thin-walled (fig. 2*a*). In our material the mean thickness of the media, expressed as a percentage of the diameter and calculated over all segments of the right lung, varied from 2.9 to 4.8 per cent in all lungs from normotensive controls older than 1 year. In the 2 youngest children (1 year old or less) these values were 5.5 and 6.3 per cent respectively. The latter finding is in agreement with the fact that thick-walled fetal pulmonary arteries only gradually diminish in size during the first 1 or 2 postnatal years of life.[5, 6] Although the media in a great majority of pulmonary arteries was thin, a certain variability occurred, so that occasionally the ratio of media to diameter was as high as 10 or even 20 per cent (fig. 2*b*). Since a small number of these exceptions could influence the mean ratio considerably, the characteristics of the distributions in all cases together are given in table 1

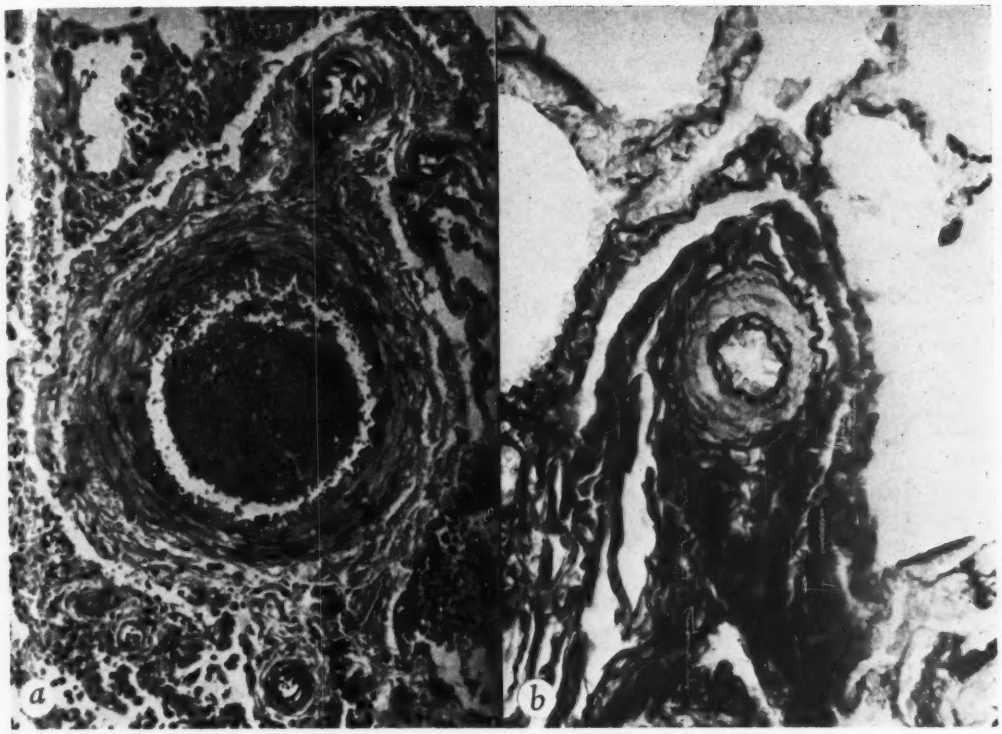

Figure 3

a. *Large muscular pulmonary artery in pulmonary hypertension (case 26, fig. 1). Medial thickening ratio of media to diameter of the artery is about 13.5 per cent (hematoxylin and eosin;* × *140.)* b. *Small pulmonary arterial branch with marked thickening of the media; the ratio of media to diameter is about 25 per cent (Weigert's and van Gieson's stains;* × *350).*

(see also figure 5). From these it appears that the peak frequency in the controls lies at 3 or 4 per cent or even lower. In the controls, no significant difference existed between the upper and lower parts of the same lung. The mean ratio for all the examined lungs was 4.3 for the upper zones, 4.4 for the middle zones, and 4.2 per cent for the lower zones. The hypertensive groups also did not differ significantly between the upper and lower regions (table 2).

The same was done for the blocks taken at the periphery of the lung and those taken at a more proximal level. For all the control lungs together both the peripheral arteries and the more proximally situated vessels yielded a mean ratio of 4.3 per cent. In the hypertensive groups the corresponding figures suggest a similar conformity of proximal and peripheral vessels (table 2).

Finally, the lingula was taken apart in 4 normotensive and 5 hypertensive cases in which the left lung was available; the mean ratio of the media of all the arteries to the diameter was calculated and compared with the corresponding groups of arteries of the left lung as a whole. The result both for normotensive and hypertensive arteries is given in table 3. No significant difference was found between the mean ratio for the lingula and that for the left lung as a whole, and the same is true for all other investigated segments.

A new division was introduced, namely, between arteries measuring less than 100 μ

Table 3

Mean Medial Thickness in Arteries in Lingula and Whole Left Lung

	Diameters of arteries			
	100 μ or more		Less than 100 μ	
	Arteries measured	Media, per cent of diameter	Arteries measured	Media, per cent of diameter
4 controls				
Lingula	71	3.9	23	5.5
Whole left lung	295	4.1	113	4.7
5 cases of pulmonary hypertension				
Lingula	47	11.8	93	12.3
Whole left lung	203	12.0	460	12.1

and those measuring 100 μ or more in diameter. This may be important as the small vessels are likely to exert more influence on the pressure in the lesser circulation than the large ones. Therefore the same division was applied to the whole group of vessels.

In all normal lungs without exception the mean ratio of the media in the small arteries was higher than that in the greater branches. For all lungs together the ratio of the former was 5.4 and that of the latter 3.9 per cent (table 4). This difference appears to be significant ($p < 0.01$; rank sign test). The same table shows the numbers of arteries in both groups which, since the vessels were taken at random, gives an indication of their frequencies as compared to each other. Arteries smaller than 100 μ are known to be relatively scarce in normal lungs. Still in 8 lungs used as controls obtained from persons more than 1 year of age, they comprised 25.8 per cent of all muscular arteries; in the 2 children less than that age they were even much more frequent (48.6 per cent) and were hardly outnumbered by the arteries of 100 μ or more in diameter. We could not confirm the finding of Heath and Best[3] that these small vessels were exceptionally numerous in the lingula. As table 3 shows, 23 vessels less than 100 μ and 71 vessels of 100 μ or more in diameter were counted in the lingula of 4 control cases; the number of small vessels is 24.5 per cent of all arteries found. Since none of these belonged to the youngest age group, this percentage is in agreement with that found for the lung as a whole.

The mean number of arteries of 100 μ or more in diameter per square centimeter of normal lung sections is given in table 5, together with the calculated mean cross-sectional area of all medial tissue in both groups of arteries per square centimeter of lung parenchyma. There was a considerable variation in the number of arteries equal to or more than 100 μ in different controls (10.5 to 20.3), but this is independent of age, perfusion of pulmonary arteries or of the localization within the lung. The same applies to the total cross-sectional area of the media in small and large arteries.

Patients with Pulmonary Hypertension

Thickening of the medial layer of pulmonary arteries is a striking feature in most cases of pulmonary hypertension (fig. 3*a* and *b*). Although occasionally it may account for 25 or even 30 per cent of the diameter of the vessel, the mean value is 4.2 to 9.2 per cent of the diameter in the moderate pressure group and 8.1 to 15.4 per cent in the high pressure group. The distribution in both groups is shown in figure 4. In the group with pulmonary systolic pressure between 30 and 80 mm. Hg, the peak frequency is shifted to the right as compared with the control group. In the high pressure group this shift is more striking, and the peak is much lower. The differences in medial thickness and frequency between normal and high pressure groups are significant for the mean ratio, standard deviation, and skewness of frequency curve; those between moderate pressure group and both other groups are partly significant (mean ratio) and partly suggestive (test of Wilcoxon). As was pointed out previously, the mean ratio of the arterial media in cases of pulmonary hypertension was independent of the site of the vessels within the lung (tables 2 and 3). Whereas in control lungs the smaller arteries had a definitely thicker media than the large arteries, in the cases of high pulmonary hypertension, where the media of vessels of both sizes is so much thicker, this difference is almost entirely lost (table 4).

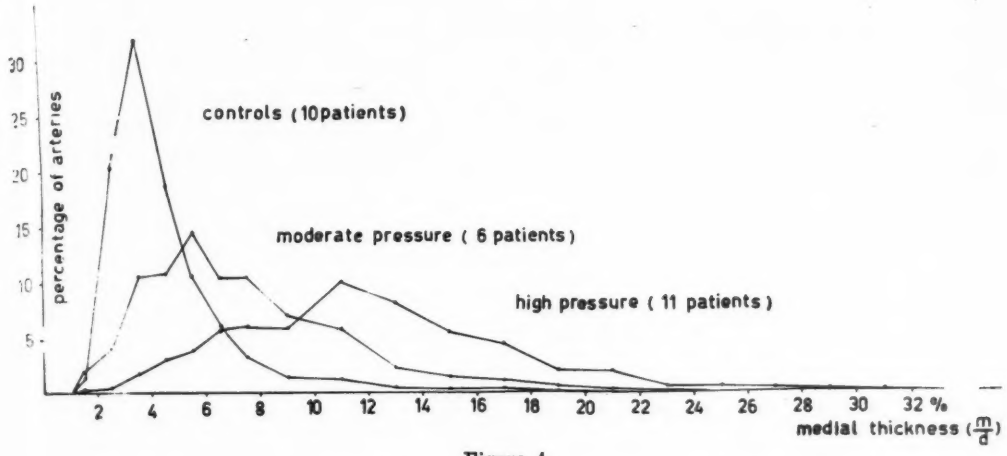

Figure 4

Distribution curve of pulmonary arteries according to their medial thickness in normal controls and in cases of moderate and of high pulmonary pressure.

The number of vessels with a diameter less than 100 μ, however, is remarkably increased to such an extent that the ratio of small and great arteries, which was about 1:3 in normal lungs, was often reversed. The cross-sectional area of medial tissue per square centimeter of pulmonary parenchyma is also raised in both small arteries and large pulmonary arteries. There is a sharp rise in surface area of the small arteries. The mean surface area of the small arteries in the high pressure group is about 5 times that in the control group (fig. 5).

The medial surface areas in both large and small arteries in normal lungs differ significantly from those in lungs with high pressure. Those in the moderate pressure group lie between, and differ significantly from, the normal, but not from the high pressure group (test of Wilcoxon) (see table 4).

Comment and Conclusions

Our finding that the mean ratio of the media to the diameter of the vessels in normal lungs is between 2.9 and 4.8 per cent, with a peak frequency at 3 to 4 or even 2 to 3 per cent, roughly corresponds with the figures of other authors. Heath and Best[3] (1958), for instance, found the ratio to be 4.2 to 5.8 per cent for arteries less than 100 μ and 2.8 to 6.8 per cent for arteries measuring between 100 to 300 μ, and Granston[7] (1958) found it to be 3 to 8 per cent, with an average of 4.4 per cent for all arteries together.

A small but rather constant number of arteries, both less than and more than 100 μ in diameter, have a thicker media than would be expected. In most normal controls one or more arteries with a ratio $\frac{m}{d} = 10$ per cent were sometimes seen, and in several of them, vessels with a media comprising 15 per cent or even more of the diameter could be found. Often such an artery had several branches that were equally thick-walled. Vasoconstriction rather than increase in the amount of muscle tissue seems likely in these cases.

No differences in medial thickness could be found dependent of the localization of the vessels, neither in hypertensive nor in normotensive lungs. Since in our cases there was no reason to assume an increased venous pressure, the almost similar figures for media in the upper and the lower parts of the lung are in agreement with the results of Doyle and associates[1] (1957), who have found such a difference only in mitral stenosis but not in their cases of congenital heart disease.

Since the medial thickness in the peripheral

Table 4

Mean Medial Thickness in Large and Small Arteries

	Diameter of arteries			
	100 μ or more		Less than 100 μ	
	Arteries measured	Media, per cent of diameter	Arteries measured	Media, per cent of diameter
Controls	1075	3.9	464	5.4
Pulmonary hypertension				
Moderate pressure	402	7.0	407	8.3
High pressure	664	11.7	1318	11.8
Significance of differences according to pressure				
Normal to moderate pressure		$T = 2.98$ $P = 0.0029$		$T = 2.01$ $P = 0.0444$
Normal to high pressure		$T = 3.77$ $P < 0.001$		$T = 3.49$ $P < 0.001$
Moderate pressure to high pressure		$T = 0.12$ $P = 0.9044$		$T = 1.58$ $P = 0.1114$

Table 5

Number of Arteries and Index of Medial Cross-Sectional Area per Square Centimeter of Lung Parenchyma in Controls and in Moderate and Severe Pulmonary Hypertension

		Mean per cm.² of lung tissue		
			Index of medial cross-section, diameter of arteries	
	Patients	Mean number of arteries	100 μ or more	Less than 100 μ
Controls	10	14.28	16,583	1694
Pulmonary hypertension				
Moderate pressure	6	11.82	34,677	3353
High presure	11	10.49	36,208	7454
Significance of differences according to pressure				
Normal to moderate pressure		$T = 1.36$ $P = 0.1738$		
Normal to high pressure		$T = 2.43$ $P = 0.0150$		
Moderate pressure to high pressure		$T = 0.65$ $P = 0.5156$		

arteries was exactly the same as that of arteries located nearer the hilum of the lung, we could not confirm the finding of Heath and Best[3] (1958) that the lingula represents an exceptional situation in so far as the thickness of the wall of the vessels is concerned. Neither the lingula nor any other of the segments investigated in this respect differed significantly from the mean value.

There was a marked difference in medial thickness between small (less than 100 μ) and larger (100 μ or more) muscular arteries: 5.4 per cent against 3.9 per cent, but this held solely for normal lungs. In hypertension this difference disappeared gradually.

The increase in thickness of the media with rise of pressure in the lesser circulation is evident. The differences between the normal and hypertensive groups in mean ratio of media to diameter of the vessels $(\frac{m}{d})$ and incidence of muscularized arterioles are significant or almost significant. This indicates a correlation between thickness of the media and degree of pulmonary hypertension. Within the high pressure group, however, this correlation was not always maintained. Often the media in the presence of high pressure, for instance 120 mm. Hg, was not much thicker or was even thinner than that in the group

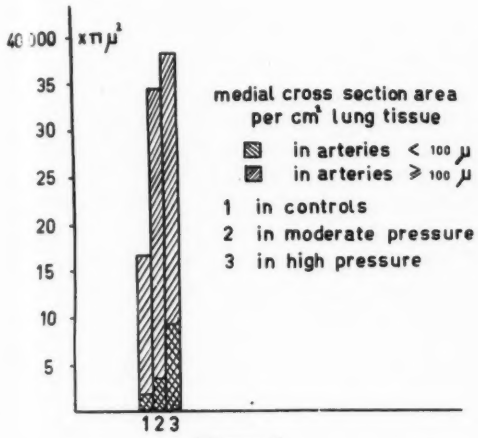

Figure 5

The mean area of media in the cross sections of arteries per square centimeter of lung tissue in controls and in cases of moderate and high pulmonary pressure.

with pressure of 80 mm. Hg. The presence of other vascular lesions such as intimal proliferation, glomerulus-like structures, and small thrombi, which are far more frequent than in the moderate pressure group, may have an additional influence on the pressure, to disturb the correlation between medial thickness and hypertension within this group.

As we have seen, a thick media might be the expression of constriction. O'Neal and associates[4] (1955) explained all thickening of the media in small pulmonary arteries in mitral stenosis in this way. An increase in the amount of muscle tissue within a certain quantity of parenchyma of the lung, however, indicates real muscular hypertrophy. This study indicates that the vascular muscle tissue both in small and large arteries is significantly raised in patients with severe pulmonary hypertension over that of normal controls.

There are more strong arguments for the occurrence of medial hypertrophy. This study indicates that in normal lungs the number of arteries of 100 μ or more in diameter is far greater than the number of small arteries (table 4). In cases of moderate pressure these numbers were about equal and in the high

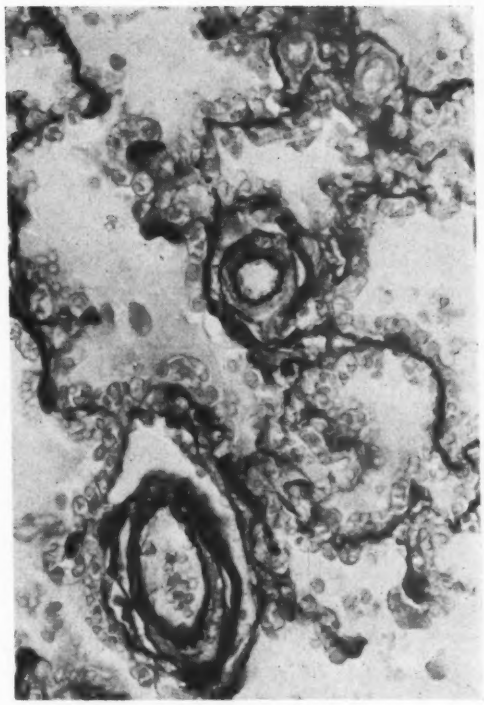

Figure 6

Arterioles in pulmonary hypertension with newly formed muscular coat (Weigert's stain and van Gieson's stain; × 350).

pressure group the small arteries were twice as numerous as the large ones. It is not possible to explain this enormous increase in arteries of the smallest category merely by a process of vasoconstriction. New muscular vessels must have been formed by the development of muscle fibers around arterioles, previously without a muscular layer (fig. 6). That this form of medial hypertrophy occurs was denied by Short[8] (1957), who considered these small arteries the result of arterial contracture, but it was accepted by Edwards[9] and Heath and Best.[3] Proof of this can be obtained from consideration of the relatively large number of arteries with a diameter of about 30 μ and a medial thickness of about 3 μ in the lungs in cases of severe hypertension. When it is recalled that as a rule the media is never less than about 2.5 μ thick,

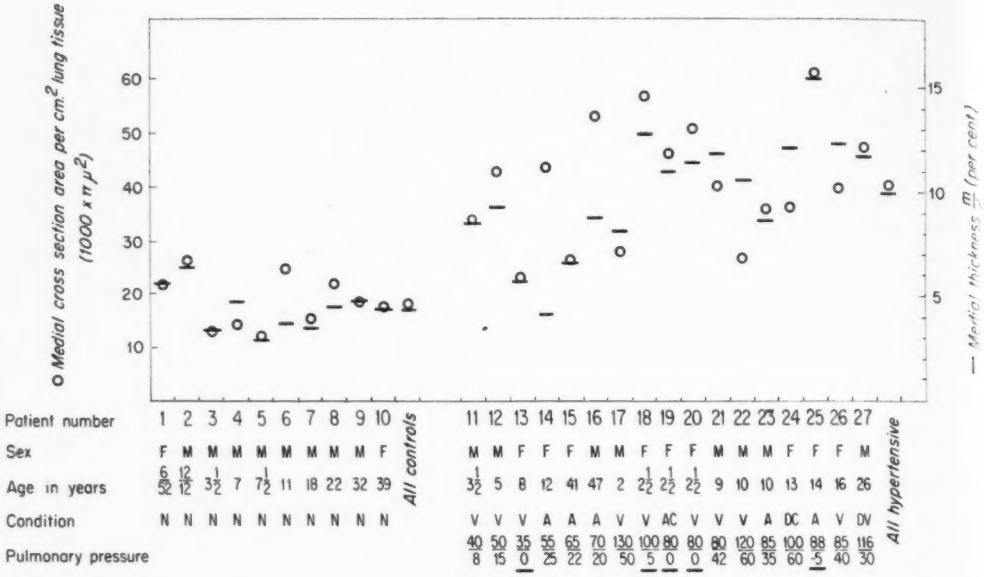

Figure 7

Diagram for comparing the index of medial cross-sectional area per square centimeter of lung tissue and the mean medial thickness in normotensive and hypertensive cases. N = normal, V = ventricular septal defect, A = atrial septal defect, AC = ostium atrioventricular commune, DC = patent ductus arteriosus and coarctation of aorta, DV = ventricular septal defect; a patent ductus arteriosus was closed 3 years prior to death. The pressures were recorded in the pulmonary artery in all except the 5 cases (underlined) in which the pressures in the right ventricle only were available. Age and sex in all cases should be noted also.

which is the thickness of one single muscle fiber, the area of the media on cross section remaining the same, such a vessel could only have arisen from an arteriole with a diameter of 35 μ and a media that was 2.5 μ thick by mere vasoconstrictive action. The diameter could not have been greater at the same cross section unless the medial thickness had decreased and this is not possible. Arteries of 35 μ or thereabout, however, are not found in normal lungs. In a similar way the largest muscular arteries provide evidence for the existence of hypertrophy of their media. Muscular arteries of about 400 μ in diameter with a media of 70 μ can be found, though not frequently, in lungs affected by pulmonary hypertension. If these vessels were products of vasoconstriction, they would have arisen from far larger arteries. A calculation shows that, if the cross-sectional area of the media remained the same and the original ratio between media and diameter were normal, that is about 4 per cent, the vessel originally must have had a diameter of about 775 μ and a media 31 μ thick. But in our control series, arteries of this size were always of the elastic and not of the muscular type. Although these findings are pointing strongly to a real increase in vascular muscle tissue, this, of course, does not mean that vasoconstriction plays no part in medial thickening. It is now fairly well established that the pulmonary arteries have a tone and are capable of constriction.

Shepherd and Wood[10] (1959) recently reviewed this topic. They concluded that a continuously increased tone, regardless of the mechanism that maintains it, probably will

lead to medial hypertrophy and although increase of tone does not necessarily cause vasoconstriction, it may cause it; therefore, the combination of medial hypertrophy and a certain degree of constriction can be expected more or less regularly. In the series studied the number of arteries of 100 μ or more in diameter per square centimeter of lung tissue showed a marked tendency to decrease in hypertensive lungs as compared with controls (table 5). The high pressure group differed significantly from the controls; the number in the moderate pressure group lay between but the difference for either group was not significant (test of Wilcoxon). Since in general vasoconstriction the diameters of all vessels tend to diminish, it might be suggested that such a constriction is responsible for this decrease in number. It is difficult to measure the degree of vasoconstriction from morphologic criteria, especially when it coincides with hypertrophy, but when a marked medial thickening is found together with a relatively low value for the medial cross-sectional area, then vasoconstriction is likely to prevail. Therefore, the medial thickness (ratio $\frac{m}{d}$) and the medial cross-surface area in all cases studied were put together in one diagram (fig. 7). That the medial thickness and cross-sectional area fell together in most cases was of course coincidence, since this depends on the choice of the scales for both factors.* It is important, however, that these two factors show a rather close correlation in controls† as well as in cases of hypertension. It may be useful to consider those cases in which a certain discrepancy exists between thickness and surface area of the media. In case 22, a case of ventricular septal defect, and in case 24 (fig. 7), a case of patent ductus with coarctation, the vasoconstriction seems to be more important than the hypertrophy, since the surface area of the media is relatively small as compared with its thickness. The reverse is found in cases 14 and 16 (fig. 7) in which a normal or moderately raised ratio of media to diameter is combined with a high cross-sectional area of the media. This suggests just the opposite of vasoconstriction, that is, passive dilatation of the vessels. It may be significant that both patients had an atrial septal defect with high flow, which could explain a certain dilatation of the pulmonary arterial system.

*The scales were chosen in such a way that the lower limit was the zero line for both factors, the upper limit was roughly the maximal value, being 60,000 as index for the cross-sectional area of the media and 15 per cent for the ratio of media to diameter.

†One of the controls (case 6, fig. 7) forms an exception in having a relatively high surface area and low ratio of the media. In the left lung of the same patient, however, this discrepancy did not exist.

Summary

To determine whether thickening of the media of pulmonary muscular arteries in cases of pulmonary hypertension is the result of vasoconstriction or of hypertrophy or of both, a method for calculating the amount of arterial muscular tissue per unit of pulmonary tissue was devised. Comparison of the mean medial thickness, expressed as a percentage of the diameters of the arteries, with the amount of arterial muscular tissue per unit of lung, will give an impression as to whether vasoconstriction or hypertrophy prevails in a certain case. This method was applied to sections of pulmonary tissue from 10 normal controls and 17 patients with congenital cardiac disease with pulmonary hypertension. Medial hypertrophy was present in all cases of congenital heart disease studied as compared with controls, and was more pronounced in severe than in moderate pulmonary hypertension. In some cases also vasoconstriction appeared to play an important or even a dominant role in the thickening of the medial layer. In 2 cases of atrial septal defect with large pulmonary flow, hypertrophy was masked by dilatation of the vessels resulting in a relatively thin media.

Acknowledgment

The patient comprising this study were from the Cardiological Department (Prof. H. A. Snellen) and the Department of Thoracic Surgery (Prof. A. G. Brom) of the Academic Hospital, Leyden (Holland).

I wish to thank Prof. Th. G. Van Ryssel (Pathological Laboratory, Leyden) for his help during these investigations and Dr. J. E. Edwards (Mayo Clinic, Rochester) for his advice and criticism after their completion. I wish to acknowledge the aid in preparing the statistical data by Mr. C. A. G. Nass and Mr. P. Van Leeuwen (Netherlands Institute of Preventive Medicine, Leyden), the technical assistance of Miss A. de Ruiter, and finally the invaluable help of Mrs. Noeke Wagenvoort in completing the calculations and tabulations.

Summario in Interlingua

Pro determinar si le spissification del media de arterias pulmono-muscular in casos de hypertension pulmonar es le resultato de vasoconstriction o de hypertrophia o del duo in combination, un methodo esseva elaborate pro le calculation del quantitate de tissu arterio-muscular per unitate de tissu pulmonar. Le comparation del spissitate medie del media (exprimite como procentage del diametro del arterias) con le quantitate de tissu arterio-muscular per unitate de pulmon permitte nos formar un idea de si, in un certe caso, il ha prevalentia de vasoconstriction o de hypertrophia. Iste methodo esseva applicate a sectiones de tissu pulmonar ab 10 normal subjectos de controlo e ab 17 patientes con congenite morbo cardiac e hypertension pulmonar. Hypertrophia del media esseva presente in omne le casos de congenite morbo cardiac studiate e esseva plus pronunciate in sever que in moderate hypertension pulmonar. In plure casos, vasoconstriction etiam pareva haber un rolo significative o mesmo dominante in le spissification del tunica medie. In 2 casos de defecto atrioseptal con marcate fluxo pulmonar, hypertrophia esseva mascate per dilatation del vasos con le resultato de un relativemente tenue media.

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Heredity

Two and two do not always make four, in the matter of hereditary descent of qualities. Sometimes they make three and sometimes five.—Oliver Wendell Holmes, M.D. *The Poet at the Breakfast Table*, 1872.

Dynamic Aspects of Cholesterol Metabolism in Different Areas of the Aorta and Other Tissues in Man and Their Relationship to Atherosclerosis

By HENRY FIELD, JR., M.D., LEON SWELL, PH.D., P. E. SCHOOLS, JR., M.D., AND C. R. TREADWELL, PH.D.

SINCE THE classical experiments of Anitschkow and Chalatow[1] accelerating the development of atherosclerosis in rabbits by feeding them cholesterol, it has been recognized that cholesterol may play an important, perhaps contributory, role in the pathogenesis of atherosclerosis in man. There are two principal hypotheses as to the source of the lipids in the atheromatous lesion.

One hypothesis is that the lipids of the aorta are derived from the plasma by infiltration. The evidence therefore has been indirect, based on a variety of associations between chemical determinations and clinical or pathologic observations. Hirsch and Weinhouse[2, 3] reviewed the literature and reported their analyses of a considerable series of aortas. They considered that unknown tissue factors are important in the causation of atherosclerosis. The composition of lipid extracts from early plaques and normal intimas that they determined was very similar to that of another large reported series of lipid extracts of plasma. They concluded that lipid deposits in atherosclerosis result from a nonselective deposition of plasma lipids.

The other hypothesis is that local synthesis is the main source of lipids in the development of atherosclerosis. This view is supported by the work of McCandless and Zilversmit,[4] who found evidence that, in the production of atherosclerosis in the rabbit, the phospholipid in the plaques is derived from synthesis within the aorta. It has also been demonstrated[5, 6] that the aorta of the calf, chicken, rabbit, and guinea pig can incorporate C^{14}-acetate into cholesterol in vitro. The aortas of men, dogs, cats, and rats have not been shown, however, to possess that ability.[6]

Extensive studies on the turnover of plasma cholesterol in man have been carried out by Biggs et al.[7-9] Hellman et al.[10, 11] and Gould and co-workers[12, 13] with the aid of labeled acetate and labeled cholesterol. Following the administration of C^{14}-acetate to man, C^{14}-cholesterol rapidly appeared in the plasma. Its free cholesterol had the highest early specific activity, and the esterified fraction did not reach equilibrium with the free portion until 2 to 3 days had elapsed. There are some partial studies dealing with the dynamic aspects of cholesterol metabolism in human tissues. Biggs and co-workers[7] reported that labeled cholesterol was detected in the aorta of a patient who died 43 days after the feeding of H^3-cholesterol. Kurland et al.[14] also found C^{14}-activity in the aorta and in a number of tissues, in 1 of 3 subjects given intravenous infusions of C^{14}-cholesterol, who died 15 days later. LeRoy and co-workers,[13] in short intervals following the administration of C^{14}-acetate and H^3-cholesterol to human subjects, found that the plasma and liver free cholesterol come into very rapid equilibrium. The cholesterol in other tissues came into equilibrium with the plasma cholesterol more slowly. Also, they found that the human adrenal synthesized cholesterol in vivo.

Because of the incompleteness of information concerning the metabolism and interchange of cholesterol in the aorta and other tissues, in man, more comprehensive studies

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Table 1

Data on Patients

Subject*	Time† (days)	Age	Weight (lbs.)	Pathologic diagnoses
Rud	2.5	69	136	Anaplastic bronchogenic carcinoma, left lower lobe, with metastases to pleura and lymph nodes; fatty infiltration of liver
Ash	8	65	133	Massive diffuse gastrointestinal hemorrhage; previously resected mucin-secreting carcinoma of stomach with extensive metastases to liver and lymph nodes
Han	18	26	137	Malignant melanoma with widespread metastases to lungs, pleura, adrenal glands, liver, etc.
Shr	27	64	—	Brain abscess following fracture of skull; purulent meningitis, healed; acute bronchitis and bronchiolitis; nephrosclerosis
Ran	38	71	94	Multiple myeloma; acute pulmonary edema
Fo	72	65	130	Anaplastic bronchogenic carcinoma, left lower lobe; metastasis to lymph nodes and brain
Wil	88	66	155	Portal cirrhosis of liver with hepatic coma and terminal thrombosis of portal vein; bronchopneumonia of left upper lobe
Ste	137	64	142	Acute recurrent myocardial infarction; arteriosclerotic heart disease; pulmonary edema

*All subjects were males.

†Represents time of death following administration of cholesterol-4-C^{14} test meal.

were indicated. This is a report of such studies, made in patients with limited life expectancies, by means of a single tracer dose of cholesterol-4-C^{14}.

Methods and Materials

Subjects

The patients were hospitalized in the medical wards at the VA Center, Martinsburg, West Virginia. All were patients whose death was expected in a reasonably short time. A summary of pertinent clinical data is shown in table 1. Of the 8 patients reported, 7 were in the same age group (64 to 71) whereas 1 was 26 years old. Seven patients died of chronic disease and were in a poor nutritional state terminally. Patient Ste died suddenly, of recurrent acute myocardial infarction, 137 days after the administration of the cholesterol-4-C^{14} meal. He was well nourished at the time of death. Those subjects died at 2.5, 8, 18, 27, 38, 72, 88, and 137 days, respectively, after the administration of the tracer dose of labeled cholesterol.

Test Meal

The cholesterol-4-C^{14} test meal was prepared by dissolving a tracer amount of cholesterol-4-C^{14} in 1 ml. of olive oil, adding 500 ml. of milk, and homogenizing the mixture. That test meal was administered in two parts, one in the morning and one in the afternoon of the same day. Seven patients received 50 μc. cholesterol-4-C^{14} and 1 subject (Wil), 75 μc.

Serum Cholesterols

Following the test meal, blood samples were obtained every day for the first 10 days and then at regular weekly intervals until death.

Treatment of Tissues and Analysis

Autopsies were performed within 6 hours after death and the following tissues were obtained: abdominal aorta, liver, kidney, heart, adrenal gland, and skeletal muscle. The aorta was freed of the tissue adherent to it, and its layers were carefully dissected along their cleavage planes into adventitia, media, and intima. The intima was partitioned, as far as occurrence permitted, into

normal-appearing portions, thickened portions or plaques, and free-lying lipid deposits, either solid (coin-like) or granular. The lipid extracts of the plasma and tissues were prepared as described earlier.[15, 16] Free and total cholesterol were determined colorimetrically on each of the plasma and tissue lipid extracts. Total lipid,[17] phosphorus,[18] and triglyceride, by difference, were determined for the different layers of the aorta and the different portions of the intima. The free and esterified cholesterol fractions of each lipid extract were precipitated as the digitonides and washed, as previously described.[15, 16] The digitonide C^{14}-activity was measured in a windowless gas flow counter and corrected for self-absorption. In some cases, it was necessary to add carrier-free cholesterol to the extract to obtain adequate amounts of the digitonides for plating. The over-all experimental error, including sample preparation and counting, was ±5.0 per cent.

Calculations

The interpretation of the results obtained in this study was based on the following considerations: that the administered labeled cholesterol was indistinguishable chemically from the endogenous cholesterol and interchanged with the tissue cholesterol, as would newly synthesized cholesterol molecules.[11] Also, it was assumed that the C^{14}-label did not enter into any other lipid fractions, since the sterol ring has been shown not to be metabolized to any appreciable extent.[19]

The free and esterified cholesterol turnover times for the various tissues were calculated from the decay portion of the tissue specific activity curves. The cholesterol specific activities of each patient (different time) were used as a point on the curve. Those calculated turnover times, while only approximations, appear to give a better index of tissue cholesterol metabolism in man than has been available previously.

The proportions of the total free and esterified tissue cholesterol derived from the plasma cholesterol fractions and by tissue cholesterol synthesis were calculated by the method outlined by Dayton,[20] in which the ratio of the peak tissue cholesterol specific activity was compared to the simultaneous serum cholesterol specific activity.

The interchanges of plasma and the cholesterol in the different layers of the aorta were calculated from the serum and tissue cholesterol specific activities data. The calculations were made at the earlier time intervals when equilibrium of the serum and tissue cholesterol had not been reached, i.e., the specific activity of the tissue cholesterol was considerably less than that of the serum cholesterol. It was then possible to integrate the area under the free and esterified serum cholesterol specific activity curves and to relate the average serum specific activity obtained to the tissue specific activity. This procedure afforded a measure of the amount of plasma cholesterol that had entered the tissue during that time. These values were then extrapolated to the time required for complete interchange of the plasma and tissue cholesterol. Such values represent the minimum degree of interchange and do not take into account tissue cholesterol synthesis nor the amount of labeled cholesterol leaving the tissue.

The free and esterified cholesterol contents of the different tissues were calculated from the average tissue cholesterol concentrations, tissue weights, and estimations of blood volume and muscle mass. The cholesterol contents of the adventitia, media, and normal-appearing intima (when sufficiently in preponderance) were estimated from the cholesterol concentrations, total weight of the aorta, and the average thickness of the different layers of the aorta. Since thickened intima and atheroma were quite variable, no attempt was made to estimate their total lipid contents.

Comment

A brief comment on the interpretation of the data presented is in order. The metabolism of these individuals, for a short time prior to their death, might be expected to have been somewhat different from that of normal persons. Although 3 of the subjects were eating poorly at the time of the administration of the test dose of cholesterol-4-C^{14}, they were all, except patient Rud, in good nutrition at that time as evidenced by small weight losses and normal serum cholesterol levels. Also, cholesterol absorption appeared to be good, as indicated by the specific activities of the free and esterified fractions of the cholesterol of the serums obtained in the early days and weeks following the administration of the test doses. Attempts were made to maintain good nutritional status, except for some defects in calories, by the liberal use of a high-protein and high-vitamin formula, by gavage, when semi-coma or other occurrences prevented a satisfactory oral intake of food. During the terminal days an adequate parenteral intake of water, glucose, and the water-soluble vitamins was maintained until a few hours before death. The average, rather than the terminal, chemical values for serum cholesterol are used for the calculations.

Table 2

Free and Esterified Cholesterol Levels in Various Human Tissues

Subjects no.	Tissue	Cholesterol, mg./Gm. wet tissue			Ester (total) %
		Free	Ester	Total	
8	liver	2.36 ±0.21†	0.51 ±0.10	2.87 ±0.24	17.8 ±2.6
8	kidney	2.50 ±0.13	0.27 ±0.05	2.77 ±0.12	9.7 ±1.8
8	muscle, ventricular	1.21 ±0.05	0.17 ±0.02	1.38 ±0.05	12.3 ±1.5
6	muscle, skeletal	0.91 ±0.06	0.07 ±0.03	0.98 ±0.06	7.1 ±1.8
8	adrenal gland	3.88 ±0.28	24.1 ±8.9	28.9 ±9.6	83.1 ±7.2
8	serum*	0.57 ±0.04	1.32 ±0.14	1.89 ±0.12	70.0 ±2.2

*Represents the average serum cholesterol level from time of administration of cholesterol-4-C^{14} test meal till death.

†Standard error of the mean.

Results

Cholesterol Concentration of Tissues

The free cholesterol concentrations in the different tissues ranged from 0.9 to 3.9 mg./Gm. wet tissue (table 2). The esterified fraction was somewhat more variable and it was highest in the adrenal gland, which had approximately 83 per cent of its cholesterol present in the esterified form.

The adventitia had a concentration of free cholesterol that was not remarkable (table 3). Its esterified cholesterol had a higher proportionate concentration (33.3 per cent of the total cholesterol) than that of other tissues except the serum, the adrenal glands, and other portions of the aorta. The concentrations of free and esterified cholesterol in the media were intermediate between those of the adventitia and those of the normal-appearing intima. The thickened intima or plaques and the free-lying lipid deposits had progressively higher concentrations of cholesterol. It is noteworthy that, of all the tissues examined in this study, except the adrenal glands, the intima of the aorta had the highest cholesterol concentrations, with a considerable portion (50 to 60 per cent) of that cholesterol in the esterified form.

Lipid Partition, Aorta

The lipid partition in different areas of the aorta is shown in table 4. In the adventitia a large proportion, 84.8 per cent of the total lipid, was present as triglyceride. The normal-appearing intima had cholesterol and triglyceride concentrations that were approximately double those of the media, whereas its phospholipid concentration was the same as that of the media. The thickened intima had concentrations of the 3 lipid fractions that were double those of the normal-appearing intima, the percentages of those fractions, in terms of the total lipids, remaining the same as those of the normal-appearing intima. The free-lying lipid deposits in the intima had the same concentrations of phospholipid and triglyceride as the thickened intima, but approximately twice the concentrations of cholesterol.

Tissue Cholesterol Specific Activities

The specific activities of the free serum cholesterol rose rapidly and usually became maximum during the first 24 hours. The labeled esterified fraction of the serum rose more slowly and did not reach maximum equilibrium until 2 to 3 days had elapsed. Thereafter, both cholesterol fractions of the serum had essentially the same specific activities. They declined, rapidly at first and then slowly.

The specific activities of the free and esterified cholesterol of the tissues obtained at necropsy, except the aorta, are shown in table 5. The free cholesterol fractions of the liver and of the serum were in equilibrium at the

earliest time (2.5 days) and they remained in equilibrium at the various time intervals thereafter. The free cholesterol fractions in the remaining tissues equilibrated with the serum free cholesterol more slowly, that of the adrenal glands following earliest.

The specific activity of the esterified cholesterol of the liver was about one third that of the corresponding fraction of the serum at the earliest time (2.5 days). The specific activities of the esterified cholesterol of the various tissues approximated that of the serum cholesterol esters at 18 to 27 days.

The specific activity curves for the free and esterified fractions of the liver are shown in figure 1. All of the points adhere closely to the curves except those for patient Ran, at 38 days, whose tracer dose was not adjusted to his unusually small size and was relatively much larger than those of the other subjects. The specific activities of all of his cholesterol samples were, accordingly, disproportionately large.

Of the portions of the aorta, only the adventitia showed C^{14}-cholesterol activity at the earliest time, 2.5 days (table 6). Its free cholesterol was in approximate equilibrium with that of the serum at 18 days. The data on the esterified fractions of the adventitia are erratic. The specific activities of both cholesterol fractions of the media were low at all times, except for that of the free cholesterol fraction of patient Ran.

The normal-appearing intima was slow in showing C^{14}-cholesterol activity. There were only traces of activity in both of its cholesterol fractions at 18 days. Both fractions attained peaks of specific activity at between 27 and 88 days (discounting patient Ran, as above). The specific activities of both cholesterol fractions of the normal appearing intima were much less than those of the corresponding sera in all of the first 7 cases. Patient Ste (137 days) will be discussed later. The specific activities of both cholesterol fractions of thickened intima were considerably less than those of the normal-appearing intima in all cases. The free-lying lipids of atheromatous deposits contained only traces of labeled cholesterol, at any time.

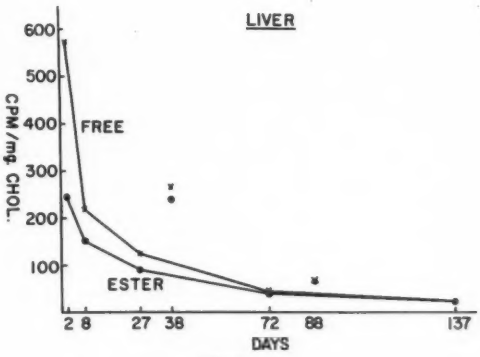

Figure 1

The specific activities of the liver free and esterified cholesterol at different time intervals following the administration of a cholesterol-4-C^{14} test meal. Each point represents a different subject.

Cholesterol Turnover

The results for the various tissues are shown in tables 7 and 8. The turnover times of the free cholesterol of the plasma ranged from 4.5 to 9 days, with an average of 8.1 days. The esterified fraction of the plasma had turnover times of 5.8 to 12.2 days, and they averaged 9.6 days. Those values are in general agreement with those reported earlier by Hellman et al.,[11] using the single-dose technic, and by London and Rittenberg, using the build-up of heavy water.[21] The specific activities of the red blood cell cholesterol fractions were not determined. Gould, Le Roy, et al.[12] found that the peak of specific activity of the erythrocyte free cholesterol was attained in man in 8 to 12 hours after doses of C^{14}-acetate. It is therefore assumed that that fraction would have about the same turnover time as that of the plasma free cholesterol. Also, the turnover times of the free cholesterol fractions of liver and plasma are not significantly different, as would be expected from the close approximation of their specific activities. The free cholesterol of the adrenal glands had a turnover time twice as long as that of the serum. The free cholesterol fractions of other tissues had much longer turnover times.

The turnover times of the free and esterified

Table 3

Free and Esterified Cholesterol Levels in Different Areas of the Human Aorta

Subjects* no.	Aorta (area)	Cholesterol, mg./Gm. wet tissue			Ester (total) %
		Free	Ester	Total	
5	adventitia	1.6 ±0.2†	0.8 ±0.1	2.4 ±0.3	33.3 ±3.5
7	media	4.0 ±0.3	3.7 ±0.7	7.7 ±0.8	48.1 ±3.8
5	intima, normal appearing	6.1 ±1.8	10.9 ±4.1	17.0 ±6.0	64.0 ±1.6
6	intima, thickened (plaques)	14.3 ±4.6	18.8 ±5.3	33.1 ±9.7	57.0 ±2.5
6	free-lying lipid material‡	31.8 ±6.3	36.0 ±7.3	67.8 ±12.2	53.1 ±4.2

*Includes only male subjects 64 to 71 years of age.

†Standard error of the mean.

‡Coin-like or granular deposits removed from surrounding tissue.

Table 4

Lipid Partition in Different Areas of the Human Aorta

Area*	Mg./Gm. wet tissue				% Total lipid		
	Cholesterol†	Phospho-lipid‡	Tri-glyceride§	Total lipid	Cholesterol	Phospho-lipid	Tri-glyceride
Adventitia	2.9 ±0.4	7.5 ±1.2	58.1 ±3.6	68.5 ±3.1	4.2 ±1.0	10.9 ±1.4	84.8 ±2.6
Media	10.2 ±1.0	8.8 ±1.0	10.7 ±1.8	29.7 ±2.6	34.3 ±2.6	29.6 ±2.0	36.0 ±2.4
Intima, normal appearing	24.4 ±6.2	10.0 ±0.9	25.6 ±4.2	60.0 ±4.7	40.7 ±3.2	16.6 ±1.9	42.7 ±3.1
Intima, thickened (plaques)	45.9 ±10.2	20.0 ±1.7	50.9 ±6.1	116.8 ±5.0	39.3 ±4.7	17.1 ±2.0	43.6 ±4.0
Free-lying lipid material	92.3 ±12.1	20.4 ±2.6	50.1 ±4.8	162.8 ±6.2	56.7 ±5.2	12.5 ±1.7	30.8 ±3.7

*See table 3 for number of subjects.

†The apparent discrepancies between the total cholesterol values in table 3 and in this table are because, in table 3, the cholesterol of the hydrolyzed ester fraction was reported as it was determined. For this table, cholesterol oleate was taken as a representative ester and the cholesterol of the ester fraction was multiplied by 1.68.

‡Phospholipid is expressed in terms of lecithin (mg P x 25).

§Triglyceride was calculated by difference.

cholesterol of the plasma were not significantly different. The turnover time of the esterified cholesterol of the liver was about twice as long as that of the plasma cholesterol esters. The turnover times for the cholesterol esters of the other tissues were much longer, although similar to those of the free cholesterol of the respective tissues, except for the adrenal glands, of which the free cholesterol turned over much more rapidly than did the cholesterol esters. In all the tissues studied, except the plasma and the adrenal glands, the turnover of free cholesterol was much greater, in milligrams per day, than that of the cholesterol esters.

The true cholesterol turnover times could not be reliably estimated from the specific activity data for the different portions of the aorta. Except for the adventitia, the delayed appearances and build-ups of C^{14}-cholesterol activities indicate slow turnovers. As explained in the footnote to table 8, estimations of the times for interchange of the cholesterol of the different portions of the aorta with that of

Table 5

Specific Activities of Free and Esterified Cholesterol of Various Human Tissues

Subject	Time* (days)	Serum		Liver		Adrenal gland		Kidney		Muscular, ventricular		Muscle, skeletal	
		Free	Ester	Free	Ester	Free	Ester	Free	Ester	Free	Ester	Free	Ester
		CPM/mg.		CPM/mg.		CPM/mg.		CPM/mg.		CPM/mg.		CPM/mg.	
Rud	2.5	582	694	572	245	266	87	89	tr†	131	tr	50	tr
Ash	8	250	263	220	151	172	78	119	74	120	38		
Han	18	136	96	118	81	105	113	93	71	137	50	62	33
Shr	27	118	98	123	90	105	119	109	85	118	72	128	102
Ran‡	38	256	268	266	239	206	269	277	172	280	207	261	204
Fo	72	50	38	42	40	31	46	45	38	41	22	44	35
Wil§	88	79	67	68	65	73	80	63	49	68	55	75	54
Ste	137	27	26	24	24	30	24	25	26	25	26		

*Represents time of death following administration of cholesterol-4-C^{14} test meal.

†tr = trace.

‡The high specific activities of the cholesterol of all patient Ran's tissues are explainable by his small size (94 lbs.) to which his tracer dose of C^{14}-cholesterol was not adjusted.

§This subject received 75 μc. cholesterol-4-C^{14}; for comparative purposes the tissue specific activities were corrected to 50 μc. in this and ensuing tables.

Table 6

Specific Activities of Free and Esterified Cholesterol of Different Areas of the Human Aorta

Subject	Time* (days)	Adventitia		Media		Intima, normal-appearing		Intima, thickened (plaques)		Free-lying lipid material		Serum	
		Free	Ester	Free	Ester	Free	Ester	Free	Ester	Free	Ester	Free	Ester
		CPM/mg.		CPM/mg.		CPM/mg.		CPM/mg.		CPM/mg.		CPM/mg.	
Rud	2.5	29	25	0	0	0	0	0	0	0	0	582	694
Ash	8	41	19	17	8			tr	tr	0	0	250	263
Han	18	119	tr†	14	tr	tr	tr					136	96
Shr	27			6	6	51	34	12	9	tr	tr	118	98
Ran‡	38			156	14	83	43			tr	tr	256	268
Fo	72	45	51	7	10			25	31	tr	tr	50	38
Wil‡	88	45	20	10	8	35	25	17	12			79	67
Ste	137	23	20	22	14	84	42	56	40	tr	tr	27	26

*Represents time of death following administration of cholesterol-4-C^{14} test meal.

†tr = trace.

‡See footnotes to table 5 for these subjects.

the serum were made. Those estimations might be equivalent to turnover times, if there were no synthesis of cholesterol in the aorta. The turnover of both free and esterified cholesterol appears to be much longer in the normal-appearing intima than in the other tissues, and still longer in the thickened, or plaqued, intima. Only traces of C^{14}-cholesterol were found in the free-lying lipid deposits of atheromata.

Discussion

The levels of free and esterified cholesterol in the different tissues, other than serum and the intima, were remarkably consistent, from individual to individual, as indicated by the small standard errors of the mean (table 2). The levels are in agreement with what scattered data are available in the literature[22] and provide a significant, coordinated addition to those data.

The chemical analyses of the lipids of the differently involved portions of the intima in this study differed from those of Weinhouse and Hirsch[3] in the considerably larger values for triglycerides obtained in this series. That difference may be explained by the different solvents and procedures used. As a result of that difference in triglycerides, the cholesterol

Table 7

Free and Esterified Cholesterol Content and Turnover of Various Tissues

Tissue	Cholesterol content			Turnover		Turnover time*	
	Free mg.	Ester mg.	Total mg.	Free mg./day	Ester	Free days	Ester days
Serum	1590	3707	5297	196	386	8.1	9.6
Red blood cell	3180		3180	393		8.1†	
Liver	3540	1430	4970	491	67	7.2	21.3
Adrenal glands (2)	35	217	252	2.3	4.2	15	52
Kidneys (2)	750	81	831	10.4	1.1	72	75
Muscle, ventricular	424	60	484	8.2	1.0	52	60
Muscle, skeletal	20177	1552	21729	310	22	65	70

*Turnover time = T1/2 × 1.44

†Assumed to be similar to that of serum on the basis of peak of specific activity in 8 to 12 hours, after doses of C^{14}-acetate, reported by Gould, LeRoy et al.[12]

Table 8

Turnover of Free and Esterified Cholesterol in Different Areas of the Human Aorta

Area	Cholesterol content			Turnover		Turnover time*	
	Free mg.	Ester mg.	Total mg.	Free mg./day	Ester	Free days	Ester days
Adventitia	40.2	20.1	60.3	0.93	0.24	43	84
Media	186.4	172.4	358.8	1.58	1.06	118	163
Intima, normal-appearing	56.7	101.4	158.1	0.35	0.46	162	221
Intima, thickened (plaques)						562	629
Free-lying lipid material						†	

*Represents time for complete interchange with plasma that would be equivalent to turnover time if there were no synthesis of cholesterol in the aorta.

†Essentially no interchange or turnover.

values, expressed as percentage of total lipids, were proportionately less in this series (table 4). The 3 lipid fractions increased proportionately with developing atherosclerosis until there were free-lying lipid deposits in the intima. In them, only the concentration of cholesterol was increased over that found in earlier plaques.

Limited studies have been reported on the dynamic aspects of cholesterol metabolism in man.[7-14] They have been mostly studies of the turnover of plasma cholesterol fractions and the equilibration of tissue and plasma cholesterol over short periods. The long periods of observation, in the present studies, were advantageous, permitting the calculation of the turnover times of the cholesterol fractions in the various tissues and the contributions of synthesis and diffusion of cholesterol to them.

The turnover times of the free cholesterol of the liver and serum were found to be approximately the same. It is assumed, on the basis of findings described above, that the turnover time of the free cholesterol of the red blood cells should be about the same as that of the plasma free cholesterol. If so, the total turnover of the free cholesterol of the liver and blood would be approximately 1.1 Gm. per day, which would represent a turnover of about 13 per cent of the free cholesterol of those tissues per day. The turnover time of the free cholesterol of the adrenal glands was also short. The turnover of the free cholesterol of skeletal muscle was 310 mg. per day but that is a very small proper-

Table 9

Contribution of Serum Cholesterol and Tissue Cholesterol Synthesis to the Cholesterol Pools of Tissues

Tissue	Source of cholesterol in tissue			
	Free cholesterol		Ester cholesterol	
	Plasma	Synthesis	Plasma	Synthesis
	% total		% total	
Adrenal gland	46	54	89	11
Kidney	77	22	68	32
Muscle, ventricular	65	35	70	30
Muscle, skeletal	88	12	94	6
Intima, normal-appearing	65	35	60	40

tion (approximately 1.5 per cent) of the free cholesterol of the striated muscle. It may be that, in the tissues where the free and esterified cholesterol have long turnover times, the cholesterol is more intimately connected with fixed elements of the cellular structure, adrenal glands and intima excepted.

Gould and his co-workers[23] have shown that synthesis of cholesterol occurred to a significant extent in a number of tissues of hepatectomized dogs after the injection of C^{14}-acetate. LeRoy et al.[13] found that adrenal gland, ovary, and skin of man, stimulated by ACTH, synthesized cholesterol from C^{14}-acetate. They did not demonstrate cholesterol synthesis in other tissues, except the liver.

This study provided data for the calculation of the contributions of plasma cholesterol to the cholesterol contents of the tissues examined (table 9). A large portion of the free cholesterol (65 to 88 per cent) of the kidney, heart, and skeletal muscle was derived from the plasma. The contributions of the cholesterol esters of the plasma to the tissues studied were on the order of 70 to 90 per cent. The rest of the cholesterol of the different tissues is presumed to have been derived by synthesis. The adrenal gland was the most active in the synthesis of free cholesterol.

The normal-appearing intima was calculated to have derived 60 to 65 per cent of both its cholesterol fractions from the plasma, leaving the remainder to have been derived by synthesis. There were insufficient usable points on the specific activity curves to make those calculations more than a fair approximation. Those of patient Ste were not used, since the specific activities of the cholesterol of his intima deviated so distinctly from those of the other patients in their relation to time and to the specific activities of the cholesterol of his other tissues. Those of patient Ran were used after correcting them for the disproportionately large tracer dose of C^{14}-cholesterol that he received, not according to his serum cholesterol, but according to other tissue cholesterols, which were so consistent from patient to patient.

The specific activities of the cholesterol fractions of thickened intima seem to indicate that a smaller portion of both its cholesterol fractions were derived from plasma. The labeled cholesterol of that portion of the intima was diluted, however, by twice as much tissue cholesterol, already present. The finding of only traces of C^{14}-cholesterol in the free-lying lipids indicates that isolated lipid deposits in the intima are relatively inert.

There has been little doubt that the liver is capable of synthesizing esterified cholesterol. It has not been determined, however, what portions of the plasma and tissue esterified cholesterol are derived from that source. In previous studies[16, 24] it was shown that in the rat a major portion of both exogenous and reabsorbed endogenous cholesterol is esterified in transit through the mucosa to the lymph. Since a large portion of the cholesterol enters the circulation by that lymph route, it may be an important source of the blood and tissue cholesterol esters in man. Also, withdrawal of

lymph cholesterol esters, via a thoracic duct cannula, markedly stimulates synthesis of cholesterol esters in tissues of the rat.[15]

The data of this study on specific activity indicate that rapid interchange of the cholesterol esters of liver and plasma does not occur. The rate of turnover of the esterified cholesterol of the liver should have been at least 10 times faster than the turnover rate that was found, if all of the cholesterol esters of the plasma were derived from the liver. It would appear that in man a major portion of ester cholesterol is formed by synthesis, during transit through the intestinal mucosa to the lymph and by synthesis in the tissues.

The data concerning the cholesterol in the adrenal gland provide information concerning the mode of synthesis of its cortical hormones. There is evidence for the existence of two distinct pathways for cortical hormone synthesis in the adrenal glands, one by direct synthesis from acetate and the other through cholesterol, as an intermediary product.[25] In this study, the turnover of free and esterified cholesterol in the adrenal glands was found to be approximately 6.5 mg. per day. The urinary steroid excretion in man has been reported to be about 24 mg. per day.[26] The present data would therefore indicate that a large portion of adrenal cortical hormone synthesis occurs directly from acetate without cholesterol being an intermediary product. The cholesterol esters of the adrenal glands, high in concentration but slow in turnover, may be of importance as a store, in reserve, which may be called upon for emergency synthesis of cortical hormones at times of stress. Long has demonstrated sharp declines in adrenal cholesterol after administration of ACTH.[27]

Patient Ste requires special consideration. At 137 days, both cholesterol fractions, from his normal-appearing and thickened intima, had exceptionally high specific activities. The data indicate that the turnover of cholesterol in his intima was much slower than it was in other patients. Only in him were the specific activities of the cholesterol fractions of the intima higher than those of the serum at necropsy.

The slow turnover of cholesterol in the intima of patient Ste seems to have been a recently acquired characteristic. A large portion of his intima had a normal appearance, and he had no gross free-lying lipid deposits in the parts of it that were examined. It does not seem probable that his intima had been absorbing and retaining unusually large amounts of cholesterol for much of his 61 years.

Patient Ste died abruptly, soon after the onset of symptoms of his second known myocardial infarction. He had received his tracer dose of C^{14}-cholesterol during a prolonged period of shock, resulting from his first known myocardial infarction, 137 days previously.

It is suggested that the prolonged turnover time of cholesterol in his intima, which seems to have been a recently acquired characteristic of unknown mechanism, might be related to the 2 known myocardial infarctions, 4½ months apart.

Variations in that unknown mechanism might explain, in part, the facts that while a large proportion of subjects who have had a myocardial infarction, in many reported series, have had increased serum cholesterol concentrations, a considerable proportion of such subjects have had normal, and some of them low normal, serum cholesterol values. A reversibility or decreased activity of that mechanism might be related, in part at least, to the long survival periods of some persons after myocardial infarction. Also, a low activity of that mechanism might be related to the low incidence of coronary disease among the heterologous subjects with familial hypercholesteremia in the very large family studied by Wilkinson and co-workers.[28]

Summary

Tracer doses of cholesterol-4-C^{14} were administered to each of 8 patients with limited life expectancies. Chemical determinations of free and esterified cholesterol and determinations of their C^{14}-specific activities were made in serially collected sera, in tissues, and in

the different layers of the abdominal aorta, the intimas of which were separated where possible, into normal-appearing intima, thickened intima, and free-lying lipid material. The turnover times of the free and esterified cholesterol fractions of the various tissues and the portions of those fractions derived from the plasma and by synthesis were calculated from these data.

The plasma and liver free cholesterol fractions were in equilibrium at the earliest time, 2.5 days. The free cholesterol fractions of other tissues were in equilibrium with the plasma free cholesterol at later dates. The esterified cholesterol fractions of the various tissues, including liver, were in equilibrium with that of the plasma at later dates than were their free fractions.

The findings indicate that a large portion of the cholesterol ester of the plasma is not derived from the liver.

The greater part of both the free and ester cholesterols of other tissues was derived from the plasma, although a significant portion was derived by synthesis, except for both fractions of skeletal muscle. The adrenal glands were the most active in the synthesis of free cholesterol.

The data indicate that a major portion of adrenal cortical hormones is synthesized directly from acetate, without cholesterol as an intermediary product.

A major portion of the cholesterol of the intima was derived from plasma through interchange but a considerable amount of cholesterol was synthesized in the intima. The free-lying lipids in the intima appeared to be inert.

Data concerning the changes of the lipid contents of the intima with the development of atherosclerosis have been presented.

One patient, who died of a second myocardial infarction, differed from the others in having a longer turnover time of the cholesterol of his intima.

Summario in Interlingua

Doses traciatori de cholesterol-4-C^{14} esseva administrate a 8 patientes con limitate superviventias probabile. Determinationes chimic de cholesterol libere e de cholesterol esterificate e determinationes de lor activitates specific a C^{14} esseva executate in serialmente colligite specimens de sero, in tissus, e in le varie stratos del aorta abdominal, con le distinction in le caso del intima del aorta—in tanto que possibile—inter specimens a apparentia normal, specimens con spissification, e libere depositos de materiales lipidic. Super le base de iste datos il esseva possibile calcular le tempores de transition pro le fractiones libere e esterificate de cholesterol in le varie tissus e le portiones de ille fractiones que esseva derivate ab le plasma de un latere e synthetisate del altere latere.

Le fractiones libere de cholesterol del plasma e del hepate se trovava in equilibrio post le plus breve intervallo, i.e. 2,5 dies. Le fractiones de cholesterol libere in le altere tissus se trovava in equilibrio con illos del plasma a tempores plus tardive. Le fractiones de cholesterol esterificate in le varie tissus, incluse le hepate, se trovava in equilibrio con illos del plasma post intervallos plus longe que le correspondente fractiones de cholesterol libere.

Le datos indica que un grande portion del esterificate cholesterol del plasma non es derivate ab le hepate.

Le plus grande parte del cholesterol libere e del cholesterol esterificate in le altere tissus esseva derivate ab le plasma, ben que un significative portion esseva formate per synthese, con le exception de ambe fractiones in le caso de musculo skeletic. Le glandulas adrenal esseva le plus active in le synthese de cholesterol libere.

Le datos indica que un portion major de hormones adreno-cortical es synthetisate directemente ab acetato, sin le occurrentia de cholesterol como producto intermediari.

Un portion major del cholesterol del intima aortic esseva derivate ab le plasma per un processo de intercambio, sed un quantitate considerabile de cholesterol esseva etiam synthetisate in le intima mesme. Le libere depositos lipidic in le intima pareva esser inerte.

Es presentate datos concernente le alterationes del contento lipidic del intima in le curso del disveloppamento de atherosclerosis.

Un patiente, qui moriva de un secunde infarcimento myocardial, differeva ab le alteres in tanto que ille habeva un plus longe tempore de transition pro cholesterol in su intima.

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Hemodynamics of Mitral Stenosis with Special Reference to Coronary Blood Flow and Myocardial Oxygen Consumption

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ALTHOUGH there are excellent articles concerning the clinical and hemodynamic features of mitral stenosis,[1-3] information concerning the coronary blood flow and the myocardial metabolism of oxygen and carbon dioxide in such subjects is inadequate. This report describes hemodynamic observations in 20 female subjects with mitral stenosis who underwent cardiac catheterization with determinations of the cardiac output and coronary blood flow.

Material and Methods

The 20 female subjects of this study were selected from the general medical wards of the University of Wisconsin General Hospital because of mitral stenosis. Many of the subjects were candidates for mitral valvulotomy and the diagnosis and degree of stenosis were confirmed at opeartion in 18 who underwent operation. One subject was not operated upon, and one (no. 14) had no clear estimate at operation of the mitral valve size. This subject has not done well postoperatively, continuing to show clinical and radiologic evidence of mitral valve obstruction.

Cardiac catheterization was done in the routine fashion on the fasting subjects. The reference point for zero pressure was half way between the anterior and posterior surfaces of the chest, measured in the region of the heart. Pressures were measured by Statham strain gages, and means were determined by electrical integration of the pressure curve. Cardiac output was measured by the Fick principle, and the coronary blood flow by the nitrous oxide saturation technic. A partition coefficient of 1 was assumed between blood and myocardium. Blood gas analyses were done by the Van Slyke-Neill technic. Expired air was analyzed for oxygen and carbon dioxide by the Scholander apparatus.

A suitable group of controls is difficult to obtain for any study such as this, but for lack of a better group we have chosen 15 normal women studied in this laboratory and previously reported.[4] Furthermore, the group of subjects with mitral stenosis were divided for comparison into those with atrial fibrillation (cases 1-7) and those with sinus rhythm.

Results

The results are summarized in table 1 for the subjects with mitral stenosis, and in the separate columns at the bottom of the page are listed the mean figures for the group of normal women along with the statistical comparison of the two groups. Although there is some overlapping, the mean age is significantly different in that our control group was younger than the group with mitral stenosis. In the absence of specific data about the influence of age on coronary blood flow no statements can be made of how this would affect the results. Surface area of the two groups was within the same range, as were the body respiratory quotient and the cardiac rate. The mean systemic arterial blood pressure was lower in the group with mitral stenosis than in the control group ($p<0.02$) and the mean pulmonary arterial blood pressure of those with mitral stenosis was higher ($p<0.01$). The wedge pressure of the patients with mitral stenosis was elevated by usual standards. The arteriovenous difference of the group with mitral stenosis was slightly greater than normal ($p<0.001$), their coronary sinus oxygen content was reduced ($p<0.02$), and their arterial-coronary sinus oxygen difference was increased ($p<0.001$). The cardiac

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Table 1

Female Patients with Mitral Stenosis

Study no.	Age	S.A.[1]	O_2[2] Cons./M.[2]	R.Q.	Card. rate	Syst.[3] MABP	M[4] PABP	M[5] Wedge	Δ^6 A-V O_2	Card. index	Tot.[7] peri. res.	L.V.[8] work index	Tot.[9] pul. res.	R.V.[10] work index	Cor.[11] blood flow	Cor.[12] vas. res.	CS[13] O_2	ΔA^{14} CS O_2	CMR[15] O_2	Card.[16] R.Q.	Index[17] effic.	Est. valve[18] diam. by surgeon
1*	43	1.6	151	0.67	48	97	26	20	5.9	2.6	1890	3.5	507	0.9	45	2.1	3.8	13.9	6.3	0.78	0.55	1
2*	41	1.7	124	0.74	58	100	29	17	5.7	2.2	2160	3.1	626	1.5	44	2.3	3.9	14.0	6.2	0.70	0.81	1
3*	41	1.6	143	0.68	102	102	25	21	4.1	3.5	1459	4.8	365	1.9	88	1.2	6.3	13.1	11.5	0.74	0.59	1.5
4*	52	1.6	151	0.68	110	79	25	17	5.2	2.8	1346	3.1	438	1.0	51	1.6	4.0	13.9	7.1	0.59	0.63	1.2
5*	29	1.5	157	0.78	72	79	29	19	5.2	3.0	1397	3.7	513	1.2	51	1.5	4.6	13.2	6.7	0.79	0.72	0.5
6*	53	1.5	132	0.94	75	86	12	9	6.4	2.0	2221	2.4	310	0.3	42	2.1	4.1	13.2	5.5	0.71	0.40	1
7*	37	1.5	138	0.93	55	76	120	29	5.5	2.4	1615	2.9	2549	4.0	45	1.8	4.4	14.1	6.3	0.84	0.62	0.9
8	36	1.6	119	0.74	96	107	22	13	4.6	2.3	2356	3.4	484	0.7	67	1.6	5.2	13.6	9.1	0.76	0.37	1
9	26	1.5	119	0.89	111	75	16	12	4.4	2.7	1482	2.7	318	0.6	77	1.0	4.8	13.8	10.6	0.63	0.26	No. op.
10	28	1.6	111	0.83	80	84	15	15	3.5	3.2	1332	3.6	239	0.7	75	1.1	5.5	11.9	8.9	0.78	0.65	1.75
11	28	1.6	123	0.82	65	74	21	20	3.5	3.5	1051	3.5	291	1.0	72	1.0	4.6	11.6	8.0	0.77	0.72	1
12	38	1.9	149	0.65	90	77	28	21	4.4	3.4	947	3.5	344	1.3	68	1.1	4.8	11.7	8.0	0.65	0.85	<1
13	41	1.7	126	0.83	80	96	30	24	3.6	3.4	1482	4.6	350	1.4	111	0.8	5.6	12.5	13.9	0.77	0.56	1
14	37	1.7	104	0.73	60	79	39	18	4.7	2.2	1682	2.4	820	1.2	44	1.8	3.6	11.1	4.4	0.83	0.47	?
15	35	1.5	134	0.93	75	71	35	16	3.9	3.4	1121	3.3	553	1.6	61	1.2	5.2	11.1	6.8	0.86	0.72	0.9
16	39	1.6	137	0.76	100	85	41	28	3.7	3.6	2720	4.2	554	2.0	74	1.2	5.2	11.6	8.6	0.75	0.79	0.5
17	28	1.4	136	0.77	71	74	32	21	5.5	2.4	1634	2.3	736	1.0	61	1.4	4.5	12.3	7.5	0.70	0.46	1
18	33	1.3	158	0.96	70	75	46	22	6.5	2.4	1873	2.5	1149	1.5	47	1.5	3.9	15.5	7.3	0.83	0.44	0.5
19	47	1.7	126	0.80	75	76	60	30	5.4	2.3	1533	2.4	1210	1.9	69	1.1	2.7	10.4	7.2	0.78	0.33	1
20	26	1.4	159	0.73	80	83	78	31	5.7	2.8	1695	3.2	1593	3.0	71	1.2	4.2	13.5	9.6	0.82	0.30	Very small
Ave.	37	1.6	135	0.79	79	84	36	20	4.9	2.8	1600	3.3	695	1.4	63	1.4	4.5	12.8	8.0	0.75	0.56	
SEM†	1.8	0.2	3.6	0.02	3.8	2.4	5.6	2.5	0.2	0.1	105	0.2	125.3	0.19	3.9	0.09	0.2	0.3	0.5	0.02	0.13	
Normal	26	1.7	132	0.79	82	92	16		3.5	3.9	1192	4.8	211	0.9	98	1.0	5.2	10.9	10.7	0.75	0.47	
SEM	1.2	0.3	2.5	0.02	1.9	1.6	0.7		0.1	0.2	60	0.2	13.4	0.05	5.4	0.07	0.2	0.3	0.6	0.01	0.02	
p	<0.001	<0.9	<0.6		<0.6	<0.02	<0.01		<0.001	<0.001	<0.01	<0.001	<0.01	<0.05	<0.001	<0.01	<0.02	<0.001	<0.01		<0.2	

* Those patients whose cardiac rhythm was atrial fibrillation.

† SEM, standard error of the mean.

1. Body surface area in square meters.
2. Oxygen consumption in ml. per min./M.^{2} of body surface area.
3. Systemic arterial mean blood pressure in mm. Hg.
4. Pulmonary arterial mean blood pressure in mm. Hg.
5. Mean pulmonary artery wedge (''pulmonary capillary'') pressure in mm. Hg.
6. Arterio-venous oxygen difference in ml. per 100 ml. of blood.
7. Total peripheral resistance in dynes cm.$^{-5}$ per second.
8. Left ventricular work in kilogram meters per minute.
9. Total pulmonary resistance in dynes cm.$^{-5}$ per second.
10. Right ventricular work in kilogram meters per minute.
11. Coronary blood flow in ml. per 100 Gm. of myocardium per minute.
12. Coronary vascular resistance in units (MABP/CBF).
13. Coronary sinus blood oxygen content in ml. per 100 ml. of blood.
14. Arterial-coronary sinus blood oxygen difference in ml. per 100 ml. of blood.
15. Cardiac metabolic rate for oxygen in ml. per 100 Gm. of myocardium per minute.
16. Cardiac respiratory quotient.
17. Index of efficiency in kilogram meters of work done per ml. of $CMRO_2$.
18. Surgeon's estimate at operation of the diameter of the mitral valve in centimeters.

index in the patients with mitral stenosis was less than in the normal group ($p<0.001$), and the left ventricular work index was reduced ($p<0.001$). The right ventricular work index, on the other hand, was increased ($p<0.05$). The total peripheral resistance in the patients with mitral stenosis was higher than in the normal subjects ($p<0.01$), and the total pulmonary resistance was likewise elevated ($p<0.01$).

As compared with the group of normal women, coronary blood flow in the subjects with mitral stenosis was reduced ($p<0.001$) as was the cardiac metabolic rate for oxygen ($p<0.01$), whereas coronary vascular resistance was increased ($p<0.01$). The cardiac respiratory quotient on the other hand was identical in the two groups and the index of efficiency, which relates the left ventricular work index to left ventricular oxygen consumption, revealed that if the left ventricular weights are presumed to be comparable, subjects with mitral stenosis had no significant difference in efficiency from the normal subjects.

The 7 subjects with mitral stenosis who had atrial fibrillation were compared statistically by the t test for each valve in table 1 with those who had a sinus rhythm. Those with atrial fibrillation were older (42 years versus 34 years, $p<0.05$), their coronary blood flow was somewhat less (52 versus 69 ml./100 Gm. L.V./min., $p<0.05$), their arterial-coronary sinus oxygen difference was greater (13.6 versus 12.4 ml./100 ml. of blood, $p<0.05$), and their coronary vascular resistance was increased (1.8 versus 1.2 arbitrary units, $p<0.01$). There were no other statistically significant differences.

Discussion

The general effect upon hemodynamics from mitral stenosis have been described by others[1-3] and reviewed recently.[3] The changes constitute chiefly an elevated wedge pressure, elevated pulmonary artery pressure, increased right ventricular work, decreased cardiac output, and increased pulmonary vascular resistance. These general hemodynamic changes are confirmed in the present study. A normal or decreased coronary blood flow has been reported previously in small groups of subjects with mitral stenosis.[5, 6] It is of interest that the coronary blood flow is reduced significantly in the presently reported group of women with mitral stenosis as compared to the normal women studied in this laboratory, but not when compared to the normal men. It is not established whether the slower coronary flow in normal men is a sex-conditioned difference, but it seems possible that coronary flow in the human subject is related inversely to body size,[4] as has been said to be the case in the dog.[7, 8] If this be true, two opposing factors would be at work in the mitral stenotic patients; their small size would tend to increase and mitral stenosis would tend to decrease coronary blood flow per unit weight of the heart. Another factor that makes it very difficult to compare subjects with mitral stenosis with each other or with any other group is that the degree of mitral stenosis varies from one subject to another. Therefore the hemodynamic effect varies, the group is not uniform, and the data tend to scatter. The variability within the group has been emphasized already by comparing those with sinus rhythm to those with atrial fibrillation.

In the present group of subjects with mitral stenosis, coronary blood flow was positively correlated with cardiac index ($r=0.67$, $p<0.01$), left ventricular work index ($r=0.65$, $p<0.01$), and the coronary sinus oxygen content ($r=0.64$, $p<0.01$). The left ventricular oxygen consumption was positively correlated with left ventricular work index ($r=0.66$, $p<0.01$), and the cardiac index ($r=0.47$, $p<0.05$), suggesting that the amount of oxygen consumed is related to the amount of work done. The results of these correlations compare favorably with those previously reported in the intact dog.[9] Furthermore, the more hemodynamically significant is the mitral stenosis in reducing cardiac output and left ventricular work, the lower is the coronary sinus blood oxygen content, and hence, presumably, the myocardial oxygen tension.

A working hypothesis would seem to be that mitral stenosis, by producing obstruction to

7. Total peripheral work in kilogram meters per minute.
8. Left ventricular work in kilogram meters per minute.

filling of the left ventricle, reduces the left ventricular output and therefore the left ventricular work. As a result, coronary blood flow and myocardial oxygen utilization are reduced. Such a hypothesis is compatible with the present data. None of the subjects of this study had true angina pectoris, although the subject with the highest pulmonary artery pressure (no. 7) had very prolonged chest pain of the variety suggesting pulmonary hypertension.[10] This particular patient had a higher mean pulmonary arterial pressure than systemic mean arterial pressure and a very reduced coronary blood flow. This flow, however, is measured per unit weight of left ventricle, and it is suspected that the pulmonary hypertensive anginoid pain may arise from right ventricular ischemia, especially when the systolic pressure generated by the right ventricle exceeds that in its perfusing coronary arteries.

Summary and Conclusions

Hemodynamic studies, including determination of coronary blood flow by the nitrous oxide method, have been reported in a group of 20 female subjects with mitral stenosis.

Pulmonary artery pressure and wedge pressure, as well as pulmonary vascular resistance and right ventricular work were increased. These subjects with mitral stenosis tended to have a lower cardiac index and left ventricular work index than did the normal subjects, and this was accompanied by a decrease in left ventricular coronary blood flow and decreased left ventricular oxygen utilization per unit of myocardial weight.

The arteriovenous oxygen difference was wider in both the systemic and coronary circulations of subjects with mitral stenosis and the coronary sinus oxygen content was lower, indicating the widespread effects of obstruction at the mitral valve.

Summario in Interlingua

Es reportate studios hemodynamic—incluse determinationes del fluxo de sanguine coronari per le methodo a oxydo nitrose—effectuate in un gruppo de 20 femininas con stenosis mitral.

Le tension del arteria pulmonar e le tension cuneate, si ben como le resistentia pulmono-vascular e le travalio dextero-ventricular, esseva augmentate. Iste subjectos con stenosis mitral tendeva a haber un plus basse indice cardiac e un plus basse indice de travalio dextero-ventricular que subjectos normal, e isto esseva accompaniate de un reduction in le fluxo de sanguine coronari sinistro-ventricular e in le utilisation de oxygeno sinistro-ventricular per unitate de peso myocardial.

Le differentia arterio-venose de oxygeno esseva plus considerabile tanto in le circulation major como etiam in le circulation coronari in le caso de subjectos con stenosis mitral, e le contento de oxygeno in le sinus coronari esseva plus basse, reflectente le extense effectos de obstruction del valvula mitral.

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Central Circulatory Changes Accompanying Mitral Commissurotomy

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OBJECTIVE evaluation of the success of mitral commissurotomy is based on knowledge of the hemodynamic changes in the pulmonary circulation and left side of the heart before and after fracture of the valve. The information currently available has been obtained primarily from pressure recordings performed at the time of commissurotomy[1-4] or from pressure recordings and simultaneous determinations of cardiac output performed weeks to months after the commissurotomy.[5-12] Although serial observations have suggested a gradual postoperative decrease in obstruction to flow across the pulmonary circulation,[5, 6, 10, 13] it has been recently proposed that the major change occurs as early as 2 to 12 weeks.[14, 15] On the basis of previous studies, however, it has been impossible to state whether the observed hemodynamic changes had occurred rapidly at the time of valve fracture or had taken place more gradually.

Although the importance of simultaneous flow measurement for proper interpretation of pressure changes has been recognized,[1, 3, 16] the determination of cardiac output at surgery has generally been neglected. The purpose of our investigation was to determine the immediate hemodynamic effects of commissurotomy by making simultaneous measurements of cardiac output and pressures at the time of operation.

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†Deceased.

Materials and Methods

The subjects were 24 patients with mitral stenosis. Atrial fibrillation was present in 9; the remaining 15 had normal sinus rhythm. None showed clinical evidence of right ventricular failure.

All patients were lightly anesthetized with nitrous oxide and oxygen or divinyl ether. A no.-18 thin-walled Cournand needle was placed in the right brachial artery before the patient was positioned for operation. After the pericardium was opened and the patient's condition had stabilized, pressures were recorded by direct puncture simultaneously from the left atrium and left ventricle and from the pulmonary artery and left atrium. A carefully measured quantity of Evans-blue dye was then injected into the left atrium; multiple blood samples were collected in a fraction collector at 1-second intervals thereafter from the indwelling arterial needle. All procedures were repeated approximately 45 minutes after commissurotomy when the patient's condition had again stabilized.

Intracardiac pressures were measured directly through no.-20 needles connected by rigid Nylon tubing to P-23D Statham strain gages, which fed into a multi-channel photographic oscillograph.* Mean pressure and diastolic pressure gradient across the mitral valve were obtained by planimetry. (Left atrial pressure was considered elevated if its mean exceeded 12 mm. Hg; 22 mm. Hg was taken as the upper limit of normal for mean pulmonary arterial pressure.)

Plasma was analyzed for Evans-blue dye with microcuvettes in a Beckman DU spectrophotometer. Cardiac output, mean transit time, and volume from injection to sampling site (*N*-*N*) were calculated from the dye-dilution curves in the manner described by Hamilton and co-workers.[17] Mitral valve area was estimated by the Gorlin formula,[18] modified for simultaneous pressure recordings in the left atrium and ventricle.[19, 20] Pulmonary vascular resistance was calculated in the usual manner.

Results

The data derived from measurements before and after commissurotomy are summarized in tables 1 and 2.

*Electronics for Medicine, White Plains, New York.

Table 1

Hemodynamic Data before and after Commissurotomy

Pt.		Age	BSA M²	Rhythm	Rate Beats/min.	LAP mm. Hg	MDG mm. Hg	LVs/D mm. Hg	PAs/D mm. Hg.		C. I. L/min./M²
G. F.	B	41	1.75	NSR	58	16	11	119/5	33/16	(24)	2.8
	A			NSR	60	7	2	135/7	30/9	(21)	2.2
F. A.	B	57	1.43	NSR	94	30	27	95/3	68/32	(42)	2.8
	A			NSR	84	9	8	94/1	38/21	(30)	2.9
O. C.	B	37	1.40	AF	88	15	9	103/6	36/21	(29)	2.3
	A			AF	89	13	7	98/6	33/18	(26)	2.6
R. D.	B	37	1.52	NSR	60	14	6	122/8	27/14	(21)	3.3
	A			NSR	60	13	4	111/9	24/14	(18)	3.5
D. E.	B	23	1.96	NSR	91	22	22	108/0			2.3
	A			NSR	92	14	11	112/3	69/32	(49)	2.7
C. G.	B	43	2.22	AF	54	17	10	110/7	49/25	(35)	2.5
	A			AF	50	13	4	120/9	42/17	(33)	2.2
N. H.	B	53	1.52	AF	50	15	9	122/6			2.7
	A			AF	49	10	2	130/8			2.2
T. H.	B	50	1.79	AF	75	19	13	127/6	44/23	(30)	2.9
	A			AF	75	8	0	130/8	33/15	(23)	3.2
V. P.	B	26	1.50	NSR	67	16	16	72/0	43/20	(28)	2.5
	A			NSR	69	13	8	77/5	35/20	(27)	2.7
F. P.	B	50	1.78	NSR	79	16	15	112/1	27/16	(21)	3.5
	A			NSR	74	11	5	109/6	23/11	(16)	3.3
L. R.	B	33	1.69	NSR	80	17	12	90/5	36/20	(26)	3.7
	A			NSR	80	10	7	100/3	31/13	(21)	4.1
A. R.	B	52	1.70	AF	62	21	13	97/7	36/21	(26)	3.3
	A			AF	57	16	7	105/9	32/18	(24)	3.3
B. T.	B	37	1.42	NSR	58	17	8	106/9	42/17	(24)	3.4
	A			NSR	55	11	2	102/9	35/11	(19)	3.0
G. Y.	B	31	1.54	NSR	68	24	20	108/4	57/27	(38)	3.0
	A			NSR	56	12	5	93/7	38/16	(26)	2.4
T. M.	B	45	1.88	NSR	94	18	15	123/3	50/27	(36)	2.2
	A			NSR	88	15	12	128/3	62/32	(41)	2.5
A. L.	B	54	1.41	AF	91	20	18	85/2	69/32	(47)	1.7
	A			AF	104	14	8	92/6	63/29	(44)	1.7
L. K.	B	37	1.39	NSR	62	22	13	115/9	78/33	(48)	1.6
	A			NSR	55	10	0	103/10	64/30	(45)	1.8
I. P.	B	37	1.56	NSR	55	16	11	90/5	30/14	(21)	3.2
	A			NSR	68	12	0	97/12	29/13	(20)	3.5
S. R.	B	46	1.44	AF	78	15	12	101/3			3.0
	A			AF	72	8	5	95/3			3.5
P. T.	B	40	1.87	AF	96	25	14	118/11			2.9
	A			AF	85	12	4	127/8			2.9
A. D.	B	55	1.76	AF	60	22	18	85/2	55/28	(39)	2.6
	A			AF	55	9	0	118/6	52/25	(36)	3.3
M. P.	B	10	.76	NSR	100	25	25	85/0			3.6
	A			NSR	106	16	10	92/6			3.2
B. L.	B	41	1.76	NSR	100	20	17	98/0	38/21	(29)	3.0
	A			NSR	70	12	5	103/4	31/18	(23)	2.4
H. A.	B	46	1.68	NSR	88	19	15	88/4	38/20	(27)	3.7
	A			NSR	73	10	7	92/5	32/17	(24)	3.2
MEAN	B				75	19	18	103/4		(31)	2.9
	A				72	12	6	107/6		(27)	2.8
Mean of individual ratios B/A					1.03	1.73	3.05	.96/.63		1.12	1.01
Significance of ratios					$p>.10$	$p<.0005$	$p<.0005$	$p>.025$ / $p<.025$		$p<.005$	$p>.35$

BSA, body surface area; LAP, mean left atrial pressure; MDG, mean mitral diastolic gradient; NSR, normal sinus rhythm; AF, atrial fibrillation; PA, pulmonary artery; LV, left ventricle; CI, cardiac index; S/D, systolic and end-diastolic pressures; B, before commissurotomy; A, after commissurotomy.

Table 2

Hemodynamic Data before and after Commissurotomy

Pt.		MVA cm.^{2}	PVR dynes sec. cm.$^{-5}$	VFP sec./min.	N-N vol. ml.	Ry/V	MVF ml./diast. sec.	1/S
G. F.	B	1.1	130	43.2	745	0.7	113	7.13
	A		254	38.2	611	1.3	100	9.02
F. A.	B	0.7	239	34.8	531	1.2	115	6.54
	A		399	31.4	773	3.1	133	5.70
O. C.	B	1.2	189	29.8	440	1.0	107	8.91
	A	1.5	212	30.0	591	2.0	123	10.37
R. D.	B	1.5	81	43.1	536	1.5	113	4.21
	A	2.1	106	43.1	686	2.3	149	6.14
D. E.	B	0.8		31.8	471	1.1	138	3.66
	A	1.8	538	28.8	346	2.5	183	2.11
C. G.	B	1.4	257	39.2	950	0.7	143	9.70
	A	2.1	326	37.9	902	2.5	130	9.95
N. H.	B	1.3		42.6	926	0.7	98	10.70
	A			36.6	605	2.3	93	6.36
T. H.	B	1.3	170	36.0	606	0.8	144	5.43
	A		205	33.0	658	1.6	175	3.95
V. P.	B	0.8	260	40.3	775	0.9	92	12.12
	A	1.3	274	38.6	965	1.5	106	11.30
E. P.	B	1.5	64	32.4	885	1.7	194	6.80
	A		67	27.4	724	2.3	214	5.67
L. R.	B	1.6	114	30.4	819	1.8	192	4.02
	A		128	27.9	759	3.8	248	3.05
A. R.	B	1.5	70	32.2	928	1.0	181	6.92
	A	2.5	109	29.0	878	1.7	204	6.75
G. Y.	B	0.9	240	40.1	640	1.4	117	5.30
	A		302	36.4	727	3.2	104	6.70
T. M.	B	1.1	342	32.0	642	1.7	127	7.84
	A	1.6	430	30.0	718	3.2	160	8.29
B. T.	B	1.5	100	37.3	585	1.1	129	6.89
	A		120	35.8	626	3.5	120	5.39
A. L.	B	0.5	900	34.3	240	1.1	65	3.50
	A	1.0	955	31.7	292	3.1	79	4.17
L. K.	B	0.5	945	32.8	385	0.8	67	11.03
	A		1120	27.5	422	1.1	91	10.82
P. T.	B	1.5		33.2	910	0.9	160	10.70
	A			32.5	930	1.5	163	9.73
I. P.	B	1.3	80	36.8	584	0.8	131	3.85
	A		112	31.3	936	6.6	175	6.75
S. R.	B	1.2		32.3	407	1.3	132	4.40
	A			31.1	443	2.0	160	4.18
A. D.	B	0.8	300	43.8	797	0.7	105	10.20
	A		366	40.2	841	2.7	147	6.24
B. L.	B	1.3	136	32.0	601	3.2	189	5.05
	A		224	30.8	575	1.8	134	6.55
M. P.	B	0.9		34.3	438	1.7	137	4.94
	A	1.6		29.7	494	2.6	141	5.41
H. A.	B	1.3	103	40.1	619	1.6	185	5.48
	A		210	36.4	655	1.8	183	5.80
MEAN	B	1.1	248	36.0	644	1.2	132.3	
	A	1.7	312	33.1	673	2.5	146.5	
Mean of individual ratios	B/A		0.74	1.09	.97	2.1	.92	
Significance of ratios			$p<.001$	$p<.001$	$.20<p<.25$	$p<.0005$	$.01<p<.025$	

MVA, mitral valve area; PVR, pulmonary vascular resistance; VFP, ventricular filling period; N-N Vol., volume from injection to sampling site; MVF, mitral valve flow.

$1/S = \frac{t_2 - t_1}{\log_{10} C_1 - \log_{10} C_2}$

Ry/V = ratio of rate of fall to the height of the V wave.

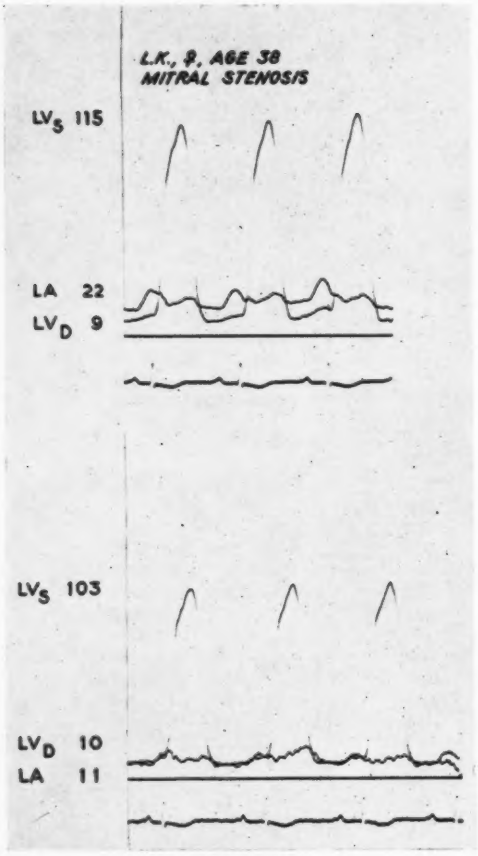

Figure 1

Simultaneous left atrial and left ventricular pressures immediately before (upper tracing) *and after commissurotomy; the diastolic pressure gradient has been completely obliterated with a resultant fall in left atrial pressure with surgery.*

Preoperative Values

All patients had normal left ventricular diastolic pressures, but their atrial pressures were elevated. The mean diastolic pressure gradient across the mitral valve averaged 17 mm. Hg.

The average left atrial V wave was 24 mm. Hg. In the 15 patients with sinus rhythm, the peak of the A wave averaged 24 mm. Hg. In 18 of the 24 cases, the ratio of the rate of the Y descent to the height of the V wave, or the Ry/v index of Owen and Wood,[21] was in the "dominant stenosis" range of 1.5 or less, in all but 1 of the remaining 6, the ratio was between 1.8 and 1.6.

Pulmonary arterial pressure was elevated to a variable degree in 74 per cent of the patients. In 3 patients who had significantly left atrial hypertension, however, pulmonary arterial pressure was essentially normal. In 17 per cent of cases, the elevation of pressure in the pulmonary artery was less than that in the left atrium, resulting in a pressure gradient across the pulmonary circulation of less than 10 mm. Hg.

Preoperative pulmonary vascular resistance ranged from 64 to 945 dynes second $cm.^{-5}$. With 1 exception (patient C. G.), a resistance greater than 200 dynes second $cm.^{-5}$ was found only in patients having a mitral valve area of 1.1 $cm.^2$ or less. Also, only 1 patient (G. F.) whose mitral valve area measured less than 1.1 $cm.^2$ had normal pulmonary vascular resistance. Thus, an appreciable increase in pulmonary vascular resistance was almost always associated with tight mitral stenosis. No definite correlation could be found between the height of left atrial pressure and pulmonary vascular resistance, except that when resistance was increased, left atrial pressure was 16 mm. Hg or more.

The average cardiac index was 2.9 L. per minute per $M.^2$ The mean for patients with atrial fibrillation was 2.7, and for those with normal sinus rhythm, 3.0 L. per minute per $M.^2$ Mean transit time averaged 8.5 seconds (S.D. = 2.3) and calculated N-N volume (needle to needle) averaged 644 ml. (range, 240 to 965 ml.).

Immediate Postoperative Changes

Left atrial pressure fell in all cases (average decrease, 8 mm. Hg). It reached a normal level in 15 cases, but dropped only to levels between 13 and 16 mm. Hg in the remaining 9. Both left atrial A and V wave peaks fell to an average level of 16 mm. Hg after commissurotomy. The Ry/v index increased in all but 1 case; the change was variable, however, and unrelated to the degree of reduction in left atrial pressure.

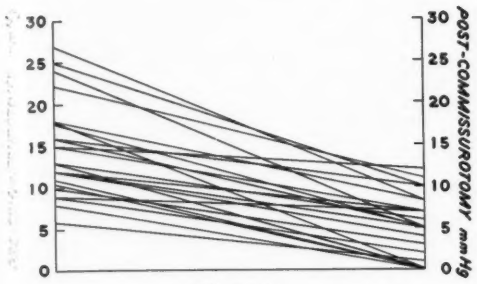

Figure 2

decrease in the mitral diastolic pressure gradient after commissurotomy was observed in all cases.

The average ventricular end-diastolic pressure rose from 4 to 6 mm. Hg. This increase was statistically significant ($p<.025$). The average decrease in mean mitral diastolic pressure gradient was 11 mm. Hg (figs. 1 and 2). The diastolic pressure gradient was obliterated in 4 of the 15 patients whose left atrial pressure fell to normal; in 11 patients there was a residual gradient of 2 to 8 mm. Hg.

Pulmonary arterial pressure decreased in all but 1 case (T.M.). In 1 of the cases (D.E.) in which a preoperative pressure was not obtained, postoperative pressure was markedly elevated. The average decrease immediately after commissurotomy was 4 mm. Hg (range, 1 to 12 mm. Hg). In the majority of cases the drop in pulmonary arterial pressure was less than the fall in left atrial pressure, resulting in a slight increase in pressure gradient between the pulmonary artery to left atrial (figs. 3 and 4). This increase resulted in a slight but significant rise in pulmonary vascular resistance.

Cardiac output showed no consistent alteration (figs. 5 and 6). The largest single increase was 27 per cent, and the largest decrease was 2 per cent of the precommissurotomy value. Changes in cardiac output and the initial severity of the mitral stenosis did not appear to be related (fig. 7). No significant change was observed in mean transit time; the preoperative to postoperative ratio averaged 0.95 ($p>0.5$). Similarly, the volume from injection to sampling site, calculated as the product of

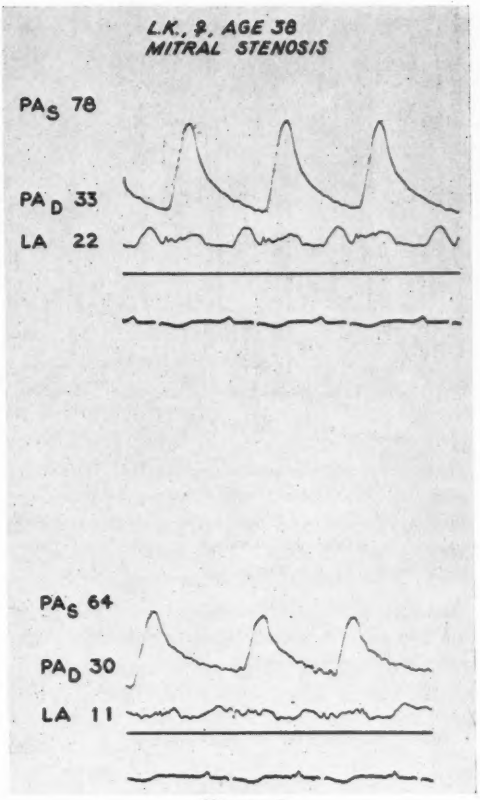

Figure 3

Simultaneous pulmonary artery and left atrial pressure immediately before (upper tracing) *and after commissurotomy demonstrates the fall in left atrial pressure after valve fracture. Mean pulmonary artery pressure, which was elevated before commissurotomy, fell somewhat less than did the left atrial pressure.*

the mean transit time and cardiac output, averaged 673 ml. and was not consistently changed.

The left ventricular diastolic filling period, or the number of seconds in each minute the mitral valve is open, decreased postoperatively (fig. 8), in all but 1 patient. The average decrease was 2.9 seconds every minute, or 8 per cent of the average preoperative value. The heart rate was essentially unchanged in 11 patients, somewhat decreased in 10 patients, and slightly increased in 3. Calculations showed that changes in heart rate could have

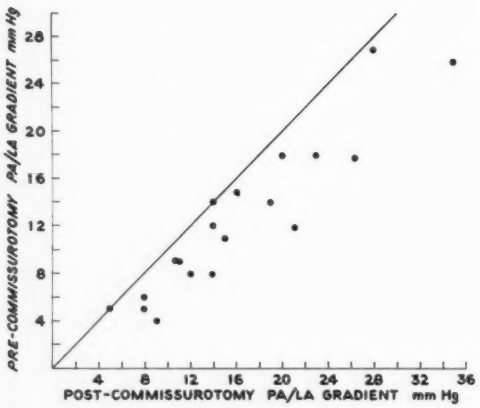

Figure 4

A consistent increase in the mean pressure gradient from pulmonary artery to left atrium was observed immediately after commissurotomy and, in the absence of a significant change in cardiac output, reflected an increase in calculated pulmonary vascular resistance.

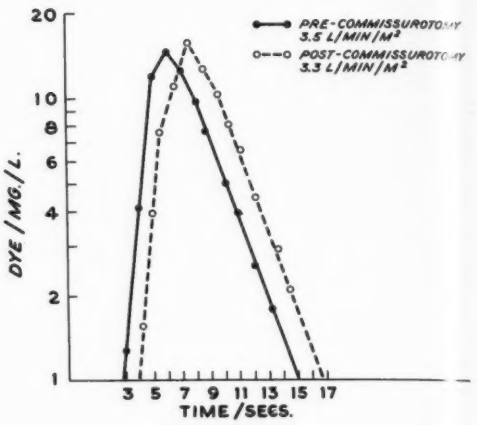

Figure 5

No significant difference between the indicator-dilution curves obtained before and after commissurotomy.

accounted for the changes in diastolic filling period in only 3 patients.

Discussion

The preoperative hemodynamic findings were similar to those previously reported in patients with mitral stenosis severe enough to require commissurotomy.[1-5, 9, 11, 13] The immediate results of valve fracture involved decreases of pressures in the left atrium, and, to a lesser extent, in the pulmonary artery, a slight rise of end-diastolic pressure in the left ventricle, but no significant changes in cardiac output.

Elevation of left atrial pressure results in passive distention of the pulmonary vascular bed and consequent lowering of the resistance to pulmonary blood flow.[22-24] If no secondary factor intervenes to produce an increase in resistance, an actual reduction may occur in the pressure gradient across the pulmonary circulation. This reduction presumably accounts for the 3 patients in our series who had essentially normal pulmonary arterial pressures preoperatively despite left atrial hypertension, and emphasizes that pulmonary hypertension, used by some,[25] as a criterion in selecting patients for commissurotomy may be absent. On the other hand, in 10 other cases, pulmonary arterial pressure was disproportionately increased in comparison to atrial pressure, due to a secondary increase in the resistance to flow through the smaller branches of the pulmonary artery.

Catheterization studies performed at intervals of weeks to months before and after commissurotomy have demonstrated varying results in regard to changes in cardiac output after the operation.[10, 11, 15, 26] On the other hand, the present study clearly reveals that no increase results immediately after valve fracture. It would appear that some factor, apart from the mechanical relief of valve obstruction, is responsible for the discrepancy between studies demonstrating an increased output and ours. Presumably, this factor is the continued immediate postoperative persistence of pulmonary vasomotor tone.

In general, the contour of the indicator-dilution curve did not change significantly after commissurotomy (fig. 5). The rate of exponential decrease in dye concentration from the left heart expressed as the reciprocals of the downstroke slopes (table 2) generally were close to those anticipated from regression equations based on cardiac outputs and N-N

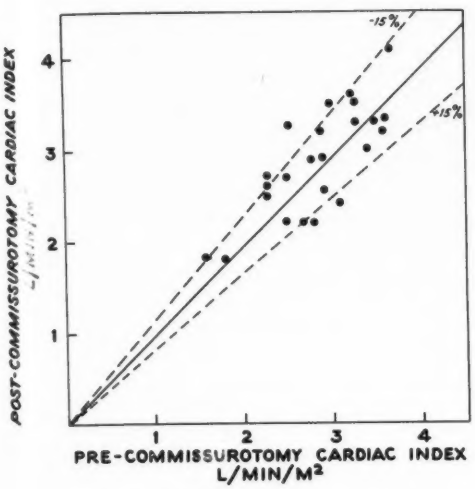

Figure 6

Cardiac output was not significantly changed immediately after commissurotomy.

volume following left atrial injection,[27] both before and after commissurotomy. This was expected in the absence of surgically produced mitral insufficiency in view of the unchanged cardiac output and N-N volume.

Since the dye was injected distally to the lungs, the N-N volume presumably reflects largely left atrial volume. Most values were in the same range observed at left heart catheterization in patients with surgically significant mitral stenosis in contrast to the larger volumes generally found with predominant mitral insufficiency.[28] The relationship between N-N volume and mitral valve area is illustrated in figure 9. Although this volume includes all portions of the arterial tree temporarily equidistant from the aortic root to the sampling needle in the brachial artery, an apparent linear relationship was observed between calculated mitral valve area and N-N volume. This would be unlikely to occur on the basis of differences in left atrial volume alone but may represent a decreasing arterial volume associated with the lowered cardiac output in severe cases of mitral stenosis. The failure of commissurotomy to affect significantly N-N volume is in accord with the absence of any change in cardiac output.

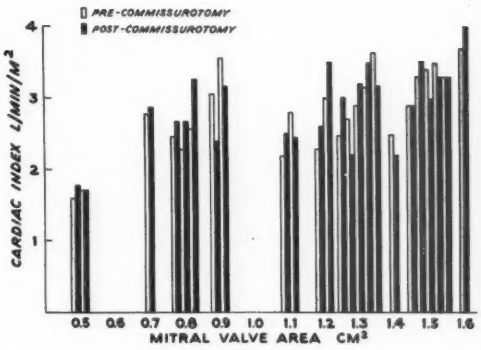

Figure 7

No relationship was observed between the change in cardiac output with commissurotomy and the initial severity of the mitral stenosis as judged by the calculated mitral valve area.

Some assessment of the effect of anesthesia and an open chest on the hemodynamic measurements was obtained by comparing the preoperative cardiac catheterization data available in 13 of the patients with those obtained at surgery immediately before commissurotomy was performed. There was no significant difference between the cardiac outputs or the left atrial pressures. The ratios of cardiac output determined preoperatively to those measured at the table immediately before commissurotomy averaged 1.09 (S.D. = .24); ratios of pulmonary artery wedge pressures from preoperative catheterization or pressures from left atrial puncture to direct left atrial pressure determined at surgery averaged 1.16 (S.D. = .29).

When left atrial pressure is elevated, ventricular filling occurs partly during isometric contraction and relaxation, and therefore, total left ventricular filling period is increased.[1, 20] With the reduction in left atrial pressure postoperatively, the diastolic filling period is decreased (fig. 8). Presumably, the ventricle then receives the same volume of blood during a shorter interval of time and the mitral valve limits the cardiac output to a lesser degree. The extension of this observation is the demonstration by postoperative cardiac catheterization[8, 15] that the primary hemodynamic result of an adequate commis-

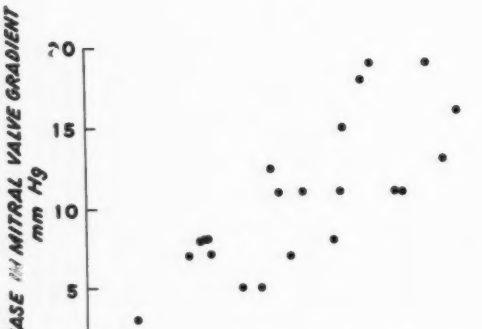

Figure 8

The duration of diastolic filling period was decreased in a linear fashion as the mitral valve gradient was reduced and left atrial pressure fell.

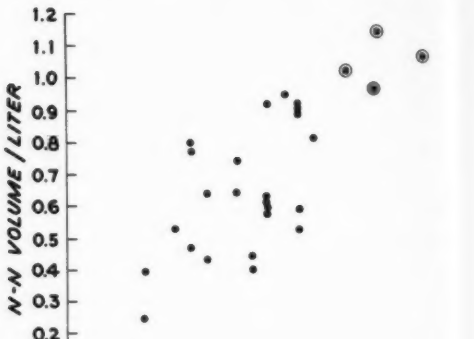

Figure 9

A linear relationship was observed between the calculated mitral valve area and the volume from injection to sampling site calculated as the product of the cardiac output and mean transit time. The encircled dots indicate 4 additional patients studied at surgery who had combined mitral stenosis and insufficiency.

surotomy is improvement in the ability of the heart to increase its output on exercise without significant elevation of left atrial pressure.

A small but significant increase in the calculated pulmonary vascular resistance occurred immediately after commissurotomy. This increase in resistance would be the expected result of the postoperative reduction in transmural distending pressure, provided there were no changes in vascular "tone."[29] Others have shown[30, 31] that the converse situation, namely an increase in pulmonary venous transmural pressure, also need not result in a change in pulmonary vasomotor "tone." It would appear, therefore, that the immediate effect of relief of mitral valve obstruction on the pulmonary circulation is limited to a reduction in distending pressure and is without detectable effect on vasomotor "tone."

The mechanism that produces the marked increase in pulmonary vascular resistance in certain patients with mitral stenosis is unknown. The increase has been variously attributed to structural narrowing of arterioles secondary to pulmonary venous obstruction[32] and to vasoconstrictive reactions in response to various unknown factors.[33-35] Recently, Semler, Shepard, and Wood[14] have offered support for a vasoconstrictive reaction as the primary mechanism on the basis of postoperative measurements during cardiac catheterization. They have shown that the major decrease in pulmonary vascular resistance occurs within 2 to 5 weeks following surgery, presumably before significant regressive organic changes could occur. On the other hand, this study shows that, whatever vasodilator reaction may occur after commissurotomy, it is not immediate. Thus, irrespective of the mechanism responsible for increasing pulmonary vascular resistance in mitral stenosis, the postoperative decrease does not seem to result immediately but occurs gradually, and no immediate direct relationship appears to exist between distending pressure and vasomotor "tone."

Summary

The flow-pressure relationships within the pulmonary circuit and left side of the heart were measured in 24 patients immediately before and just after mitral commissurotomy. The diastolic pressure gradient across the mitral valve was decreased in all cases, but was

rarely obliterated completely. No significant change occurred in cardiac output; a shorter ventricular filling period and a consequent increase in mitral valve flow per unit of filling time was consistently observed. A decrease in mean pulmonary artery pressure generally occurred with valve fracture, but it was almost always less than the decrease in left atrial pressure. The result was an immediate postoperative increase in the pressure gradient and in the calculated resistance across the pulmonary circuit. These observations suggest that the reduction in left atrial pressure following mitral commissurotomy has no immediate effect on pulmonary vasomotor tone.

Acknowledgment

The authors express their appreciation for the complete cooperation extended by the Department of Surgery, without which this study could not have been accomplished.

Summario in Interlingua

Le relation inter fluxo e tension intra le circuito pulmonar e le latere sinistre del corde esseva mesurate in 24 patientes immediatemente ante e post le effectuation de commissurotomia mitral. Le gradiente del tension diastolic trans le valvula mitral esseva reducite in omne casos, sed su oblitteration complete esseva rar. Nulle alterationes significative occurreva in le rendimento cardiac. Un plus curte periodo de replenamento ventricular e un consequente augmento del fluxo mitral in le unitate de tempore de replenation esseva observate uniformemente. Un reduction del tension medie del arteria pulmonar occurreva generalmente con le fractura valvular, sed iste reduction esseva quasi semper minus marcate que le reduction del tension sinistro-atrial. Le resultato esseva un augmento immediatemente post-operatori in le gradiente de tension e in le calculate resistentia trans le circuito pulmonar. Iste observationes pare indicar que le reduction del tension sinistro-atrial que seque commissurotomia mitral exerce nulle effecto immediate super le tono vasomotori del pulmon.

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Renal Hemodynamic Responses to Stress in Normotensive and Hypertensive Subjects

By C. T. Bello, M.D., R. W. Sevy, Ph.D., M.D., E. A. Ohler, Ph.D., C. A. Papacostas, Ph.D., and R. M. Bucher, M.D.

THE PRESENT investigation was undertaken as part of a larger study intended to provide additional information about the pathophysiology of essential hypertension. A great deal of valuable information pertaining to the pathophysiology of this disease has been obtained by numerous investigators and has been critically summarized.[1-4] Many of the pertinent studies designed to reveal the basic hemodynamic alterations were necessarily conducted under more or less standard resting conditions, e.g., postabsorptive state, supine position, etc. Much less is known about these alterations as they exist during normal daily activity, i.e., during the major portion of each day. Further studies under these conditions would appear to be of particular importance, since abnormal blood pressure responses to such stimuli as cold, pain, physical exercise, hyperventilation, breathholding, and inhalation of irritants and of carbon dioxide, have been reported in hypertensive patients.[5] Abnormal pressor and depressor responses to tilting,[6] and exaggerated pressor and cardioaccelerator responses to psychologic stress[7] have also been reported for hypertensive patients. Hypertensive and normotensive subjects show essentially the same variety of patterns of acute responses with regard to cardiac output, blood pressure, and peripheral resistance, when subjected to "stress interviews," but the hypertensive subjects were observed to differ from normotensive subjects by more frequently and more or less chronically displaying a "high resistance" pattern.[8] A more frequent incidence of the "resistance" type of response in hypertensive subjects has also been observed during application of the combined stimulus of the cold pressor test and mental arithmetic.[9] The possible relation between these responses to environmental and psychologic stresses, and the pathogenesis of essential hypertension has been repeatedly discussed,[7, 8, 10] and responses to some of these stimuli have been proposed as a possible means of distinguishing prehypertensive from normal individuals.[7, 10] Increased sensitivity of peripheral blood vessels to the vasoconstrictor action of epinephrine or norepinephrine in the hand,[11] bulbar conjunctiva,[12] and nail fold[13] has been observed in hypertensive patients. Doyle and Black[14] observed greater pressor responses to angiotonin, s—methyl-isothiourea, and norepinephrine in hypertensive than in normotensive subjects. On the other hand, Judson and coworkers[15] found no qualitative or quantitative differences between hypertensive and normotensive subjects in their pressor responses to single intravenous doses of epinephrine.

A knowledge of the responses of hypertensive patients to various environmental stimuli has practical as well as theoretical importance, e.g., in defining the status or adequacy of a given function during exposure to such stimuli. Both experimental and clinical evidence directs attention to multiple measures of function in hypertensive disease (cardiovascular, renal, neurogenic, endocrine, etc.), and quantitation of responses in all of these measures to a variety of stimuli would be desirable. The present report is concerned chiefly with renal hemodynamic responses to mild stresses in hypertensive, as compared with normotensive subjects. Only 2 such stresses or stimuli are presently considered: exercise (sit-ups), and cold (cold pressor test). Renal responses to various environmen-

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tal stimuli in normotensive and hypertensive subjects have been reported[16-21] and provide a basis for the selection of effective stimuli. With the exception of emotional stress, however,[20, 21] most studies have not usually involved sufficient numbers of both normotensive and hypertensive subjects to permit an adequate quantitative comparison of their renal responses to such stimuli.

Methods

Twenty-eight normotensive and 51 hypertensive patients were selected for the study from hospital and outpatient populations of Temple University Hospital. The majority of patients in each group was from the clinic rather than from private practices. All the hypertensive patients were studied previously and followed for periods varying from months to years by one of the authors (C. T. B.). Diagnosis was based on the usual clinical criteria (history, physical examination, urinalysis, blood chemistries, funduscopic examination, Fishberg concentration test); special tests were performed only when judged necessary to clarify the diagnosis (phenolsulfonphthalein excretion test, intravenous pyelograms, urea clearance, retrograde pyelograms, Regitine test, histamine test). Blood pressures in excess of 150/90 mm. Hg were required for inclusion in the hypertensive group; the large majority displayed diastolic blood pressures persistently above 100 mm. Hg. Patients displaying evidence of complications such as congestive heart failure, angina pectoris, or cerebral vascular accidents were excluded. In 43 of the hypertensive patients the diagnosis was "benign" essential hypertension; in 8, malignant hypertension.

The normotensive patients were selected with special care to exclude major illness and conditions that might conceivably alter renal function; none was seriously ill at the time of the study.

Both groups were selected to include both sexes, Negro and white races, and to encompass young, middle aged, and elderly adults. The normotensive group ranged in age from 15 to 68 years, and included 15 women (5 Negro and 10 white) and 13 men (3 Negro and 10 white). The hypertensive group ranged in age from 21 to 64 years, and included 32 women (23 Negro and 9 white) and 19 men (11 Negro and 8 white).

All subjects were studied in the morning in the postabsorptive state, and were given 500 to 700 ml. of water orally just prior to the study. Except where specified, all medications were withheld at least 1 to 2 days prior to the study; due regard was given to the known durations of actions of the medications being given. Measurements for each patient were made during 2 control periods in the supine position, during the period of stress and during 2 or more recovery periods in the supine position. The duration of each period was usually 10 minutes, but was occasionally longer (10 to 20 minutes). The renal clearance procedures were essentially those described by others.[1, 22] A constant volume (20 ml.) of sterile distilled water was used as a bladder rinse in addition to air. A "delay period" of 6 minutes was assumed in calculating mid-point plasma values for inulin and para-aminohippuric acid (PAH). PAH was determined chemically by the methods described by Smith.[22] Inulin was determined by the method of Bojesen,[23] except that accurately graduated test tubes were covered with marbles rather than tight stoppers during boiling; accurate reconstitution to the original volume was made with absolute ethanol after boiling. This modification still allowed excellent conformity with Beer's law, whether determined in aqueous solution or in plasma, and plasma yield studies revealed recoveries ranging from 98.5 to 101 per cent. The inulin equivalent of glucose is small by this method and can be corrected by subtraction of a plasma blank, provided large fluctuations in blood sugar do not occur during the study. As a check against this possibility, the patients were examined for glucosuria, and periodic blood glucose determinations were made in several subjects submitted to each of the two stresses. As determined by this method, the average inulin clearance (C_{in}) in the normotensive subjects in this study was somewhat lower than the accepted normal value. The range of values for C_{in} was 54 to 142, with lowest values occurring in the older patients. However, 68 per cent of the normotensive subjects had control values for C_{in} within 116.5 ± 28.1, the normal value for mixed sexes derived from several sources by Smith.[17] The clearance of inulin (C_{in}) was used as a measure of glomerular filtration rate, and the clearance of para-aminohippurate (C_{pah}) as a measure of effective renal plasma flow. Renal blood flows were derived from PAH clearances and hematocrit values. Clearance values were corrected to a body surface area of 1.73 M.^{2} Blood pressure was measured prior to and one or more times during each clearance period by the auscultatory method, and mean blood pressure (P_m) was calculated as diastolic pressure plus 40 per cent of the pulse pressure. Blood pressures were measured as frequently as possible during the period of stress: before and after each group of sit-ups during the period of exercise stress, and at approximately 1-minute intervals during the cold pressor test. The mean pressure for the period of stress was taken as the average of all individual readings during the period. Total renal vascular resistance (R_t) was calculated as the

ratio of mean blood pressure (mm. Hg) to renal blood flow (ml./sec.).

The stresses were applied during period three of the renal clearances, and were as follows: (1) exercise, consisting of the maximum number of sit-ups tolerated by each patient during a 10-minute period (the range of sit-ups for each group was similar, and the mean number of sit-ups as follows: normotensive, 107; benign essential hypertensive, 86; malignant hypertensive, 78; sympathectomized hypertensive, 92); (2) cold pressor test, as described by Hines,[24] performed twice during a 10-minute period. The selection of these stresses was arbitrary. They are, with minor qualifications similar to normal environmental stimuli; they are convenient to apply; and they produce alterations in renal function. The cold pressor test is a noxious stimulus in addition to a localized cold stimulus. The particular exercise of sit-ups involved postural and intra-abdominal pressure changes in addition to exercise. When exercise is performed as the maximum tolerable number of sit-ups, fatigue also becomes a factor to consider. The use of the terms "exercise" or "cold" stress is not intended to exclude these other factors.

The patients studied during reserpine therapy had been receiving reserpine at a dose of 0.1 to 0.25 mg. 3 to 4 times daily for a period of 4 weeks or longer.

The technic employed for surgical sympathectomy was the Peet procedure.[25]

Results

Responses to Exercise

The responses to the exercise of sit-ups in renal clearance period 3 are shown for normotensive and benign essential hypertensive groups in table 1. The data presented for each period are *group* averages. Numbers in parentheses refer to the number of patients in each group. Statistical comparisons of the maximal responses to exercise between normotensive and hypertensive groups are shown in table 2; "maximal response" refers to the difference between control value (mean of periods 1 and 2) and the value at the height of the response (period 3 or 4) for each patient. The data presented in table 2 are averages of these maximal responses for each group.

The untreated hypertensive subjects had, for 3 weeks or more prior to the study, received no antihypertensive drug except phenobarbital, which was discontinued 1 or 2 days prior to the study. The sympathectomized hypertensive subjects were studied 7 days to 3 years after sympathectomy. A comparison of the maximal responses in these 4 patients before, and 7 to 107 days after, sympathectomy is shown in table 3. As a group, the sympathectomized hypertensive subjects were judged, on the basis of clinical studies, to have more severe disease prior to sympathectomy than the patients in the other hypertensive groups.

As shown in table 1, all 3 hypertensive groups displayed lower control values for the clearances of inulin and PAH and higher control values for filtration fraction, mean arterial pressure, and renal vascular resistance, in comparison with the normotensive group. On the other hand, the average pattern of response to exercise was similar in normotensive and hypertensive groups: decreases in renal clearances, and increases in filtration fraction, mean arterial pressure, and renal vascular resistance. This general pattern of response was satisfactorily consistent, with the exception of some of the treated or sympathectomized hypertensive subjects. None of the 16 normotensive persons and only 1 of the 8 untreated hypertensive patients failed to show a definite decrease in C_{pah}, and only 1 of each group failed to show a definite increase in renal vascular resistance. Changes in C_{in} were less uniform, 3 of the 16 normotensive and 1 of the 8 untreated hypertensive subjects showing only a slight or negligible decrease, and 2 of the normotensive and 1 of the hypertensive group showing slight or negligible increases.

There were certain quantitative differences between groups. As shown in table 2, the untreated and reserpine-treated hypertensive subjects showed a significantly greater increase in renal vascular resistance than did the normotensive ones. Also, the reserpine-treated hypertensive group showed a tendency, although not statistically significant, to respond less than the untreated hypertensive group. The *interpretation* of quantitative changes in renal vascular resistance, however, is another matter (see Discussion).

In the majority of the sympathectomized hypertensive subjects the renal responses to

Table 1

Responses to Exercise (Sit-ups) Applied in Period Three (Mean ± Standard Error)

Period	C_{in}	C_{pah}	FF	P_m	R_t
			Normotensive (16)		
1	95 ± 4.83	608 ± 44.75	0.1624 ± 0.0092	102 ± 2.5	6.07 ± 0.61
2	100 ± 5.67	635 ± 40.75	0.1622 ± 0.0092	99 ± 2.9	5.63 ± 0.48
3	92 ± 4.86	535 ± 42.75	0.1787 ± 0.0085	107 ± 3.9	7.21 ± 0.74
4	87 ± 4.51	461 ± 31.50	0.1945 ± 0.0100	98 ± 3.1	7.58 ± 0.73
5	96 ± 5.41	550 ± 24.25	0.1776 ± 0.0095	98 ± 3.4	6.07 ± 0.43
6	93 ± 5.90	546 ± 23.80	0.1717 ± 0.0101	99 ± 3.3	6.18 ± 0.44
			Hypertensive — Untreated (8)		
1	80 ± 15.51	444 ± 59.01	0.1818 ± 0.0156	163 ± 6.1	13.81 ± 1.66
2	89 ± 11.52	482 ± 73.14	0.1924 ± 0.0109	162 ± 6.3	13.17 ± 1.88
3	73 ± 7.31	351 ± 54.72	0.2143 ± 0.0100	175 ± 7.9	20.00 ± 3.16
4	73 ± 6.04	340 ± 37.46	0.2169 ± 0.0114	163 ± 7.2	18.16 ± 2.87
5	87 ± 13.67	476 ± 74.20	0.2171 ± 0.0076	161 ± 6.5	13.79 ± 2.66
6	91 ± 4.29	435 ± 69.80	0.2116 ± 0.0102	160 ± 8.9	14.65 ± 3.58
			Hypertensive — Reserpine treated (9)		
1	75 ± 14.60	361 ± 31.07	0.1817 ± 0.0174	149 ± 4.6	15.03 ± 2.25
2	66 ± 7.50	338 ± 26.17	0.1831 ± 0.0173	151 ± 6.0	16.60 ± 2.84
3	63 ± 7.83	303 ± 22.29	0.1856 ± 0.0186	165 ± 7.9	19.99 ± 2.40
4	62 ± 8.73	282 ± 24.66	0.1950 ± 0.0174	154 ± 8.1	17.34 ± 1.47
5	76 ± 13.70	333 ± 41.76	0.1906 ± 0.0199	153 ± 6.0	19.24 ± 4.93
6	72 ± 6.75	393 ± 42.06	0.1904 ± 0.0181	154 ± 7.4	13.44 ± 1.42
			Hypertensive — Sympathectomized (8)		
1	70 ± 11.7	361 ± 43.77	0.1908 ± 0.0153	164 ± 11.7	18.97 ± 4.38
2	69 ± 6.7	358 ± 31.80	0.1947 ± 0.0140	159 ± 6.2	16.77 ± 2.08
3	62 ± 7.8	319 ± 30.39	0.1992 ± 0.0104	164 ± 8.6	20.13 ± 2.32
4	73 ± 6.4	349 ± 32.51	0.2169 ± 0.0160	158 ± 6.4	17.40 ± 1.42
5	77 ± 9.2	378 ± 38.87	0.2095 ± 0.0176	160 ± 6.8	17.44 ± 3.36
6	91 ± 15.6	449 ± 78.57	0.2072 ± 0.0180	164 ± 8.8	15.63 ± 3.95

C_{in}, inulin clearance; C_{pah}, para-aminohippuric acid; FF, filtration factor; P_m, mean blood pressure; R_t renal vascular resistance.

exercise were minimal. The effect of sympathectomy on these responses is best shown in table 3 for the 4 patients studied both before and after sympathectomy. The results were consistent in each of the 4 patients.

Responses to Cold Pressor Test

The responses to the cold pressor test in renal clearance period 3 are shown for normotensive and benign essential hypertensive groups in table 4. The data for each period are group averages. Statistical comparisons for maximal responses are shown in table 2. Again the hypertensive subjects showed lower control values for renal clearances, and higher control values for filtration fraction, mean arterial pressure, and renal vascular resistance. In general the renal responses to this stimulus were less marked than, but just as consistent as, the responses to exercise. Quantitative differences in the responses between the normotensive and hypertensive subjects were also not so great as they were with exercise (table 2). While the result was not statistically significant, the untreated hypertensive subjects again showed a greater average increase in renal vascular resistance. The reserpine-treated group showed a definite tendency to respond less than untreated hy-

Table 2

Maximal Responses to Stress in Normotensive (N), Untreated Hypertensive (H) and Reserpine Treated Hypertensive (H-R) Subjects (Mean ± Standard Error)

	N (16)	H (8)	H-R (9)
Stress = exercise			
C_{in}	— 13 ± 3.0	— 21 ± 7.6	—13 ± 3.4
C_{pah}	—168 ± 30.8	—151 ± 45.8	—69* ± 16.8
P_m	+ 6 ± 2.3	+ 13 ± 4.1	+15 ± 5.1
R_t	+ 2.2 ± 0.4	+ 7.0† ± 2.1	+ 4.9† ± 0.7
	N (12)	**H (14)**	**H-R (9)**
Stress = cold pressor test			
C_{in}	— 10 ± 4.2	— 11 ± 2.8	—11 ± 3.9
C_{pah}	— 95 ± 17.9	— 85 ± 17.9	—43* ± 24.5
P_s	+ 27 ± 3.3	+ 36 ± 4.5	+43 ± 7.8
P_d	+ 26 ± 4.5	+ 26 ± 3.3	+22 ± 4.4
R_t	+ 1.7 ± 0.2	+ 3.7* ± 1.0	+ 2.0 ± 0.8

*Difference from normotensive is of borderline significance ($p = >0.05; <0.10$).
†Significant difference from normotensives ($p = <0.01$).
See table 1 for key to abbreviations.

pertensive subjects. In this experiment the 9 treated patients were selected from the untreated group, and were, therefore, studied both before and during treatment. The control values (periods 1 and 2) were unaffected by treatment. However, the tendency for reserpine to reduce the magnitude of the renal responses (C_{pah}, R_t) to the cold pressor test was observed in 7 of the 9 patients. Pressor responses to the cold pressor test did not appear to be reduced by reserpine, however. There was no significant difference in either the systolic (P_s) or diastolic (P_m) pressor responses between the normotensive and either of the hypertensive groups.

The sympathectomized hypertensive patients showed minimal renal responses to the cold pressor test, as was the case for exercise stress. Three patients were subjected to the cold pressor test both before and after sympathectomy; the results were consistent in each of the 3 patients (table 3). While the pressor responses were unaffected, the renal responses were considerably reduced by sympathectomy.

Table 3

Maximal Responses of Hypertensive Subjects to Stress before and after Sympathectomy

	Stress = exercise (4)		Stress = cold pressor test (3)	
	Before	After	Before	After
C_{in}	— 20	— 6	—13	— 6
C_{pah}	—158	—40	—92	—15
P_m	+ 12	+ 9	+10	+12
R_t	+ 10.7	+ 3.6	+ 6.3	+ 1.6

See table 1 for key to abbreviations.

Responses of Malignant Hypertensive Patients

The responses of patients with malignant hypertension to the stress of exercise are shown in table 5. The majority of patients in this group, whether treated or untreated, showed little or no response to exercise. One additional patient studied both before and after sympathectomy did respond to the cold pressor test before sympathectomy with decreases in renal clearances and increases in filtration fraction, mean arterial pressure, and renal vascular resistance. These responses were abolished by sympathectomy. The control values (periods 1 and 2) for the malignant hypertensive group showed more severe departures from normal than did the control values of the benign hypertensive groups.

Discussion

The findings of reduced renal clearances of inulin and PAH, and elevated renal vascular resistance during control periods in the majority of essential hypertensive, as compared

Table 4

Responses to Cold Pressor Test Applied in Period Three (Mean ± Standard Error)

Period	C_{in}	C_{pah}	FF	P_m	R_t
			Normotensive (12)		
1	96 ± 8.47	590 ± 49.71	0.1661 ± 0.0085	98 ± 4.1	6.73 ± 0.95
2	98 ± 6.44	592 ± 41.91	0.1677 ± 0.0080	100 ± 4.0	6.09 ± 0.63
3	94 ± 8.09	549 ± 41.33	0.1714 ± 0.0072	110 ± 3.8	7.55 ± 0.66
4	90 ± 7.28	513 ± 37.28	0.1742 ± 0.0068	100 ± 3.4	7.49 ± 1.02
5	98 ± 5.81	538 ± 38.15	0.1843 ± 0.0064	102 ± 3.3	7.24 ± 0.71
6	95 ± 7.00	521 ± 29.77	0.1800 ± 0.0080	101 ± 3.7	7.16 ± 0.48
			Hypertensive — Untreated (14)		
1	79 ± 2.77	441 ± 21.3	0.1822 ± 0.0085	151 ± 5.2	12.33 ± 0.83
2	75 ± 2.57	438 ± 20.6	0.1753 ± 0.0071	148 ± 5.2	11.87 ± 0.83
3	78 ± 4.29	430 ± 34.6	0.1901 ± 0.0096	160 ± 5.5	13.97 ± 1.43
4	69 ± 4.51	365 ± 28.1	0.1930 ± 0.0069	145 ± 4.7	14.70 ± 1.26
5	69 ± 4.45	368 ± 20.3	0.1884 ± 0.0068	145 ± 4.9	14.11 ± 1.08
6	76 ± 4.61	403 ± 28.4	0.1925 ± 0.0080	146 ± 4.9	13.65 ± 1.48
			Hypertensive — Reserpine Treated (9)		
1	87 ± 5.3	415 ± 20.5	0.2097 ± 0.0123	148 ± 7.3	12.44 ± 0.86
2	90 ± 4.6	432 ± 22.8	0.2118 ± 0.0123	148 ± 6.1	12.15 ± 0.68
3	86 ± 7.9	414 ± 31.3	0.2068 ± 0.0137	157 ± 6.1	13.50 ± 0.83
4	81 ± 1.9	386 ± 25.9	0.2106 ± 0.0080	149 ± 6.7	13.47 ± 0.52
5	88 ± 5.7	397 ± 24.6	0.2134 ± 0.0070	145 ± 4.8	12.39 ± 0.91
6	88 ± 2.8	397 ± 23.8	0.2215 ± 0.0070	148 ± 5.5	12.64 ± 0.96
			Hypertensive — Sympathectomized (4)		
1	64 ± 11.75	329 ± 54.2	0.1921 ± 0.0355	158 ± 8.7	19.92 ± 4.99
2	59 ± 10.70	306 ± 50.8	0.1861 ± 0.0122	158 ± 7.5	22.25 ± 4.99
3	70 ± 11.85	379 ± 61.4	0.1858 ± 0.0111	170 ± 10.1	18.77 ± 4.77
4	55 ± 7.90	304 ± 44.8	0.1811 ± 0.0084	156 ± 7.7	22.45 ± 4.81
5	73 ± 18.53	393 ± 107.0	0.1884 ± 0.0081	155 ± 8.3	20.24 ± 4.83
6	73 ± 14.76	380 ± 71.5	0.1898 ± 0.0044	157 ± 8.0	18.57 ± 3.40

See table 1 for key to abbreviations.

with normotensive subjects were expected on the basis of previous reports.[1, 26, 27] In the majority of hypertensive subjects in this study both C_{in} and C_{pah} were reduced below the mean value for the normotensive group, but C_{pah} was nearly always reduced proportionately more than C_{in} with a resultant increase in filtration fraction. Only 6 of the 51 hypertensive patients had control values for C_{in} at or above the mean value for the normotensive group. Only 1 of 51 hypertensive patients had a control value for C_{pah} at or above the mean value for the normotensive subjects, and renal vascular resistance in this patient was well below the normotensive mean.

Quantitative comparison of the renal responses to stress between normotensive and hypertensive subjects was the major object of this investigation. The general pattern of the responses to such stresses in both normotensive and hypertensive groups was known beforehand. Quantitatively, the similarities in the renal responses to stress between normotensive subjects and those with benign essential hypertension were more striking than the differences. Both normotensive and untreated hypertensive groups responded to exercise

Table 5

Responses of Malignant Hypertensives to Exercise Applied in Period Three (Mean ± Standard Error)

Period	C_{in}	C_{pah}	FF	P_m	R_t
			Untreated (4*)		
1	54 ± 21.90	159 ± 56.3	0.269 ± 0.0650	172 ± 5.1	48.60 ± 27.45
2	58 ± 15.20	166 ± 50.1	0.258 ± 0.0475	173 ± 4.5	47.14 ± 25.46
3	54 ± 11.05	136 ± 41.4	0.304 ± 0.0595	184 ± 4.9	58.07 ± 29.09
4	60 ± 15.10	145 ± 24.5	0.316 ± 0.0530	175 ± 1.8	51.89 ± 25.13
5	66 ± 14.10	161 ± 53.4	0.303 ± 0.0460	171 ± 2.7	47.27 ± 23.23
6	57 ± 11.90	144 ± 40.0	0.294 ± 0.0440	170 ± 2.4	53.62 ± 28.08
			Reserpine Treated (3)		
1	43 ± 23.5	197 ± 168.5	0.189 ± 0.0595	171 ± 5.4	59.59 ± 33.88
2	35 ± 15.7	191 ± 62.2	0.173 ± 0.0618	162 ± 7.3	33.14 ± 10.42
3	35 ± 17.9	186 ± 85.0	0.164 ± 0.0537	155 ± 14.6	38.22 ± 13.92
4	39 ± 20.5	189 ± 72.8	0.173 ± 0.0595	164 ± 6.9	40.16 ± 17.84
5	39 ± 18.0	214 ± 69.9	0.167 ± 0.0526	162 ± 3.0	29.52 ± 10.67
6	35 ± 23.4	225 ± 65.1	0.235 ± 0.0000	162 ± 1.6	24.72 ± 10.63

*P_m and R_t determined for only 3 patients.
See table 1 for key to abbreviations.

and to cold with similar changes in C_{in} and C_{pah}. When compared with respect to changes in renal vascular resistance, the hypertensive subjects appeared to respond with greater increases than did the normotensive ones. A similar difference between the renal responses of normotensive and hypertensive subjects has been observed during the application of emotional stress.[20, 21] The question arises whether or not this hyperreactivity in terms of renal vascular resistance should be interpreted as renal *vascular* hyperreactivity. The answer to this question depends upon the definition of "vascular hyperreactivity." Hines[10] used the term "vascular reactivity" as meaning a quick rise in blood pressure unassociated with an increase in cardiac output, and considered to result from increased peripheral resistance produced by vasoconstriction. He defined as "vascular hyperreactors" those persons with usually normal blood pressure who show marked reactions in diastolic pressure to various stimuli. Other investigators have implied the existence of vascular hyperreactivity in hypertension on the basis of greater reductions in blood flow,[11] and visible constriction of blood vessels[12, 13] in response to vasoconstrictor stimuli. As pointed out by Redleaf and Tobian,[28] however, increased vascular responsiveness in terms of blood pressure, blood flow, vascular resistance, or visible blood vessel constriction may be more apparent than real. If one considers vasoconstrictor responses in terms of vascular smooth muscle shortening, it is apparent from Poiseuille's law that an equivalent degree of smooth muscle shortening would cause a far greater increase in resistance to flow in the already narrowed vessels of hypertensive subjects, than in the vessels of "normal" diameter in normotensive subjects.[28, 29] In addition, in the presence of changing flows and pressures, changes in blood viscosity are not inconsiderable in determining vascular resistance.[30] Finally, in determinations of pressure head, venous pressures are often not available, as was the case in this study, and hence true pressure gradients are not often used in calculating resistance. The authors conclude that a greater than normal change in renal vascular resistance in response to a given stimulus is not in itself evidence of renal vascular hyperreactivity.

Perhaps a more important conclusion from

the results of this study is that hypertensive patients, even though they show reduced values initially, respond to the stresses of exercise and the cold pressor test with as marked reductions in glomerular filtration rate and renal plasma flow as do the normotensive ones. In hypertension, therefore, these functions may be more severely compromised during most of a 24-hour day than is indicated by resting values.

The results also indicate that sympathectomy reduces or abolishes the acute renal responses to these stresses without necessarily affecting resting values. The results suggest that the *responses* are mediated, at least in part, by the sympathetic nervous system. Diminution or reversal of the renal responses to the cold pressor test[10] and to emotional stress[20] following sympathectomy has been reported. Wilkins and co-workers,[19] however, observed no effect of splanchnicectomy on the renal responses to venous congestion of the limbs. Reserpine, which acts centrally to suppress some sympathetic responses, also appears to diminish the renal responses to the stresses of exercise and the cold pressor test in the majority of hypertensive patients. Reserpine did not affect control or resting values, however. Procedures that effectively and consistently prevent or reduce these responses to stress might be expected to improve renal function as it exists during normal daily activity. This point requires further investigation.

The relative lack of responsiveness in the majority of patients with malignant hypertension may be due either to a more nearly maximal vasoconstriction initially or to organic vascular disease rendering the vessels unresponsive.

Summary

Renal responses to stress were studied in 28 normotensive and 51 hypertensive patients. Renal clearances of inulin and PAH, filtration fraction, arterial blood pressure, and renal vascular resistance were determined in each patient immediately before, during, and after exercise (sit-ups), or the cold pressor test.

In the control periods immediately before stress the majority of patients with essential hypertension displayed reduced values for inulin clearance (C_{in}) and clearance of para-aminohippurate (C_{pah}) and increased values for filtration fraction and renal vascular resistance, when compared with normotensive groups. These abnormalities were more severe in malignant hypertension than in benign essential hypertension.

The pattern of response to stress was similar in normotensive and untreated hypertensive patients: reduction in C_{in} and C_{pah}, and increases in filtration fraction, blood pressure, and renal vascular resistance. These responses were more marked with exercise than with the cold pressor test. These responses to stress were also quantitatively similar in normotensive and untreated hypertensive subjects, except for renal vascular resistance, which was increased more in the hypertensive groups. Hyperreactivity in terms of vascular resistance, however, is not necessarily indicative of vascular smooth muscle hyperreactivity.

The renal responses to exercise or the cold pressor test were reduced or abolished in hypertensive subjects by sympathectomy, and were diminished, in the majority of patients, by therapy with reserpine. Neither sympathectomy nor reserpine affected control (prestress) values for renal clearances or renal vascular resistance, however.

The majority of patients with malignant hypertension, though showing severely reduced values for C_{in} and C_{pah}, and marked elevations in renal vascular resistance initially, showed minimal renal responses to exercise or the cold pressor test.

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Summario in Interlingua

Le responsas renal a stress esseva studiate in 28 patientes normotensive e 51 con hypertension. Le valores del clearance renal de inulina e de acido para-aminohippuric (PAH), le fraction de filtration, le tension del sanguine arterial, e le resistentia renovascular esseva determinate in omne caso individual immediatemente ante, durante, e post exercitio (sit-ups), o le test del pressor frigide. Le responsas renal a stress esseva studiate in 28 patientes normotensive e 51 con hypertension. Le valores del clearance renal de inulina e de acido para-aminohippuric (PAH), le fraction de filtration, le tension del sanguine arterial, e le resistentia renovascular esseva determinate in omne caso individual immediatemente ante, durante, e post exercitio (sit-ups), o le test del pressor frigide.

jacer ad seder) o le application del essayo cryo-pressori.

Durante le periodos de controlo immediatemente ante le stress, le majoritate del patientes con hypertension essential monstrava reducite valores in le clearance de inulina (C_{in}) e le clearance de para-aminohippurato (C_{pah}) e elevate valores pro le fraction de filtration e le resistentia reno-vascular in comparation con le patientes normotensive. Le anormalitates esseva plus sever in hypertension maligne que in hypertension essential benigne.

Le modo del responsa al stress esseva simile in patientes normotensive e in nontractate patientes hypertensive, i.e., illo comprendeva reductiones de C_{in} e C_{pah} e augmentos del fraction de filtration, del tension de sanguine, e del resistentia reno-vascular. Iste responsas esseva plus marcate con exercitio que con le essayo cryo-pressori. Le mentionate responsas a stress esseva etiam simile in lor valores quantitative in subjectos normotensive e in nontractate subjectos hypertensive. Le sol exception de iste regula esseva le resistentia reno-vascular que se monstrava plus marcatemente elevate in in le gruppo hypertensive. Tamen, hyperreactivitate in le resistentia vascular non reflecte necessarimente hyperreactivitate del parte del musculo lisie del vasos.

Le responsas renal a exercitio o al essayo cryo-pressori esseva reducite o abolite per sympathectomia in subjectos hypertensive. In le majoritate del patientes illos esseva reducite per administrationes therapeutic de reserpina. Ni sympathectomia ni reserpina afficeva le valores de controlo (de ante le stress) pro le clearances renal o le resistentia reno-vascular.

Le majoritate del patientes con hypertension maligne—ben que illes monstrava severmente reducite valores pro C_{in} e C_{pah} e marcate elevationes del resistentia reno-vascular sub conditiones de controlo—manifestava responsas minimal a exercitio e etiam al essayo cryo-pressori.

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On Cardiac Murmurs

By AUSTIN FLINT, M.D.

The physician who undertakes to interrogate the heart by auscultation is not to decide that the condition of his patient is alarming, simply because he finds a murmur which he satisfies himself is dependent on an organic lesion of some kind. The lesion may be at that time, and perhaps ever afterwards, innocuous; the evils arising from cardiac affections may be remote, and so far from plunging the patient into despair by the announcement of the fact that he has an incurable disease of heart, there may be just grounds for holding out expectation of life and comfortable health for an indefinite period. Neither does it necessarily alter the case when more than one murmur is discovered; the existence of several murmurs by no means excludes the possibility of similar encouragement. We are to look to other sources of information than the murmurs in forming an opinion respecting the gravity of the affection.—*Am. J. M. Sc.* n.s. **44**: 29, 1862.

Response to Exercise in Congenital Complete Atrioventricular Block

By DANAE IKKOS, M.D., AND JOHN S. HANSON, M.D.

THE CLINICAL and hemodynamic findings in patients with complete heart block have been reported by many authors.[1-14] There is general agreement that irrespective of the etiology of the block, cardiac enlargement and increased stroke volume are the compensatory mechanisms for the slow rate. In a few studies ventricular rate and other hemodynamic changes have been followed during exercise.[1-3, 13-15] The prevailing opinion is that in patients with the congenital form of complete heart block the ventricular rate increases more readily than in patients with the acquired form of the arrhythmia. This opinion is based principally on observations in isolated cases. Therefore, the effect of exercise and exercise tolerance were studied in patients with the congenital form of complete atrioventricular dissociation.

Materials and Methods

The present studies were conducted in 11 such patients ranging from 7 to 23 years of age. Diagnosis of congenital A-V block had been made in infancy or early childhood in all patients. Exhaustive histories had failed to disclose any infective, toxic or other bases for the supposition that the blocks might be acquired rather than congenital. None of the patients had subjective cardiac symptoms, including Stokes-Adams attacks.

Exercise tolerance tests were performed on an electrically braked bicycle ergometer* for 2 6-minute periods. The work load during the first period was approximately half the submaximal working capacity as predicted on the basis of the patient's physical characteristics (sex, age, and body weight).[21] During the second period the full load was applied. In the usual calculation of the submaximal working capacity the load causing a pulse frequency of 170 per minute at a relatively steady state is taken as the desired value.[16, 17] In the present series such a reference value could not be obtained because of the patients' cardiac arrhythmia. Therefore, in duplicate determinations each subject was asked to perform exercise at increasing loads up to his limit of tolerance. The highest work load tolerated was arbitrarily taken as the submaximal working capacity. During exercise additional correlative signs proposed by others[14] such as atrial heart rate and electrocardiographic changes were followed.

A standard 12-lead electrocardiogram was recorded at rest. During exercise the electrocardiogram was obtained by placing the indifferent electrode on the forehead. Heart volume was determined radiologically by means of biplane, right angle radiographs.[18, 19] Predicted normal values in standing position were calculated according to Maurea.[20] Total amount of hemoglobin was determined by the alveolar carbon monoxide method[22] with certain modifications.[23] Total blood volume was calculated from total hemoglobin and hemoglobin concentration. Right heart catheterization was performed according to methods previously described from this laboratory.[24] Oxygen content and capacity of blood samples were determined by Van Slyke manometric apparatus, while oxygen saturation of cardiac catheter samples was determined in a Kipp Haemoreflector according to Brinkman.[25]

Results

The primary data concerning heart size, working capacity, electrocardiographic findings, and total amount of hemoglobin as well as atrial and ventricular rates before, during, and after exercise are presented in table 1. The heart size, relative to body size, is presented graphically in figure 1. Since the age and body size of the patients varied widely, the relative heart size is presented as the difference between the found heart volume (in standing position) and the one predicted on the basis of the data of Maurea,[20] the difference

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*Manufactured by Elema Corporation, Stockholm, Sweden.

Table 1

Clinical and Hemodynamic Data

Case no.	Sex	Age	Height (cm.)	Weight (Kg.)	Body surface area ($M.^2$)	Heart volume (ml.)		Total amount (Hb g)	Working capacity (Kg./min.)	Pulse rate										Electrocardiographic abnormalities during exercise
										Rest		Exercise				After exercise				
												1st load		2nd load		1 min.		5 min.		10 min.	
						Standing	Prone			A	V	A	V	A	V	A	V	A	V	
1	F	23	171	57	1.67	570	830	585	600	81	41	125	67	160	72	111	50	97	45	94	44	—
2	M	19	178	68	1.83	1030	1310	755	700	43	43	88	48	143	64	77	52	43	43	48	45	bigeminy
3	M	17	179	57	1.74	800	945	730	900	80	55	130	100	170	130	150	88	112	66	112	67	few extrasystoles
4	M	16	171	70	1.81	990	1210	800	900	84	46	111	54	170	120	160	60	97	42	90	40	bigeminy
5	F	15	163	64	1.69	770	710	450	500	97	50	136	57	176	68	176	60	120	56	120	54	bigeminy
6	M	14	142	38	1.23	455	570	455	700	94	60	125	69	166	94	127	72	112	62	112	62	—
7	F	12	140	34	1.30	350	—	370	400	82	46	138	98	185	128	160	78	113	53	102	48	—
8	F	11	154	38	1.15	541	505	350	400	100	50	136	66	170	90	158	79	118	58	118	58	bigeminy
9	M	10	137	28	1.05	340	520	300	400	86	54	120	64	160	92	97	57	100	54	90	54	few extrasystoles
10	F	8	139	36	1.18	560	680	370	350	109	56	150	80	176	102	158	70	115	58	109	58	—
11	F	7	118	20	0.81	356	440	265	200	97	52	158	78	176	83	136	57	99	49	107	50	—

Figure 1

Heart volume, ml., (in standing position) in relation to body size, expressed as the difference between observed and predicted values in σ-units; predicted values from Maurea et al.[20]

being expressed in standard deviation units. Definite cardiac enlargement was found in 5 of the 11 cases. In figure 2 the heart size (heart volume in prone position) is plotted against the total hemoglobin. When this reference standard was used definite cardiac enlargement was present in 7 of 10 cases.

Figure 3 shows that the patients' physical working capacity was not correlated to their heart size and that in 6 of 10 patients working capacity was normal, being only slightly reduced in 4.

During work all patients showed increases in both atrial and ventricular rates (fig. 4). In 6 cases extrasystoles appeared during exercise, and in 3 of these 6 bigeminy or trigeminy was observed during short periods, usually at the maximal load. One patient, accustomed to strenuous exercise and with a ventricular rate of 36 to 40 per minute at rest, developed bigeminy and trigeminy during the second work load. This disappeared during continued exercise, and a ventricular rate of 130 per minute was present at the end of the work period.

The ventricular rates observed during exer-

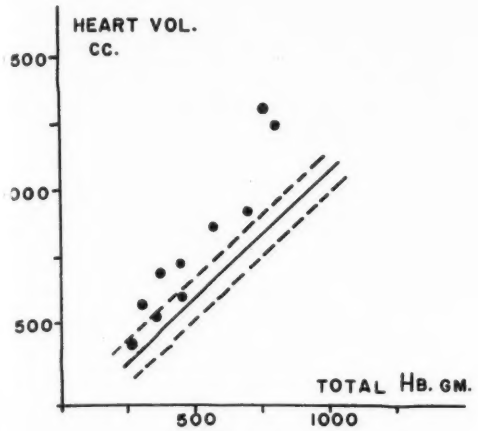

Figure 2

Heart volume, ml., (in prone position) in relation to total amount of hemoglobin. Normal values and their ± 2σ limits from the data of Holmgren et al.[29]

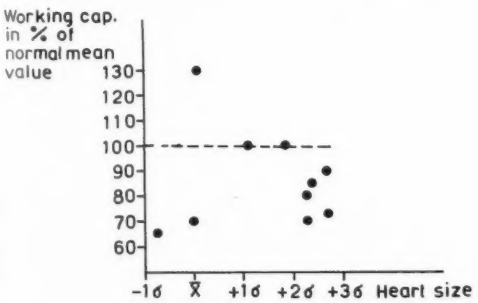

Figure 3

Working capacity in per cent of the normal value (normals from Bengtsson[21]) related to heart size expressed in standard deviations.

cise, disregarding periods with extrasystoles, varied between 68 and 130 per minute. No correlation between the ventricular rate at rest and that during exercise was established (fig. 5). Nor was there any correlation between heart size and ventricular rate (fig. 6). When the exercise was stopped, extrasystoles disappeared immediately in 4 patients and within 1 minute in another. In the sixth instance the bigeminy, which appeared during the test, persisted for 5 minutes after exercise. This particular patient had at the same time a sinoatrial block and demonstrated the largest degree of heart volume increase observed in the present group. Because of the sinoatrial block this patient has been excluded from figures 5, 6, 7, and 10.

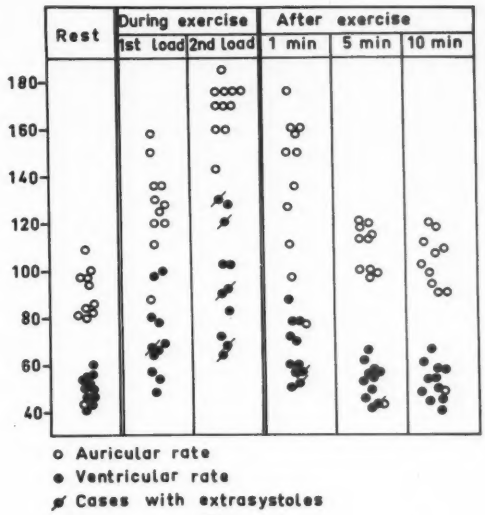

Figure 4

Atrial and ventricular rates at rest, during and after exercise.

The relative increase in the atrial and ventricular rates during exercise are shown in figure 7. The former increased almost stepwise at increasing work loads, but a stepwise increase in ventricular rate was found in only a few cases. In several instances the maximal ventricular increase occurred between rest and the first load, while in others it was observed during the second load.

Although it was previously assumed[14] that in congenital heart block the relation between the atrial and ventricular rates remained unchanged by exercise, this was not, however, the case in our material. Changes in the ratio of atrial-ventricular rates were observed in every case, being pronounced in 3, both during (fig. 8) and after exercise (fig. 9).

The relation between the gain in the atrial and ventricular pulse rate during exercise (in per cent of the rate at rest) is presented in figure 10. The present findings demonstrate a clear positive correlation between these 2 variables, the gain in the ventricular rate in-

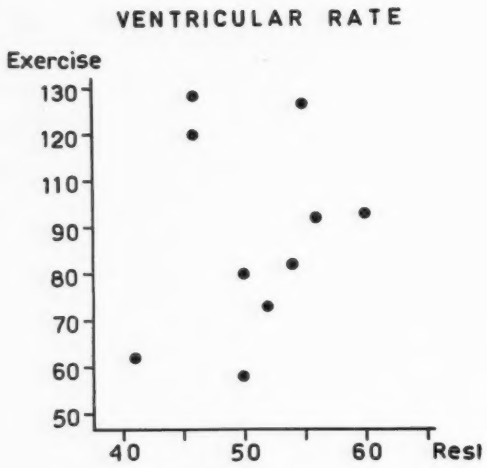

Figure 5

The relation between the ventricular rates at rest and exercise.

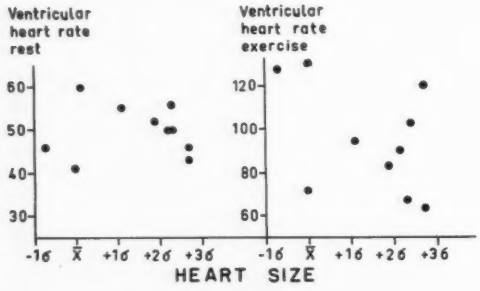

Figure 6

Relation between ventricular rate at rest and exercise and relative heart size (expressed in S.D. from normal).

creasing parallel with the gain in the atrial rate.

Upon cessation of exercise atrial and ventricular rates decreased and returned almost to previous values within 10 minutes (fig. 4). The rapidity with which this decrease occurred was, however, not always the same for the 2 rates. In most instances the ventricular rate decreased more rapidly than the atrial as is shown by the increase in the atrial-ventricular ratio 1 minute after exercise (fig. 9).

Cardiac catheterization was carried out in 4 of the 11 subjects, evidence of an atrial septal defect being found twice (table 2). All right

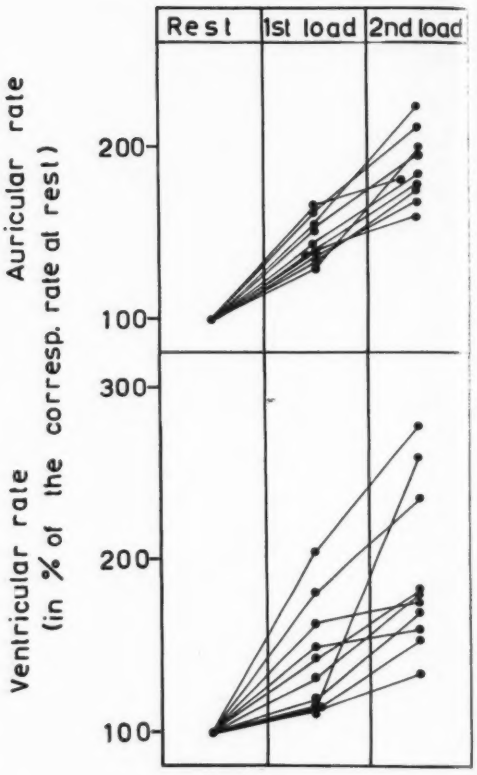

Figure 7

The change in atrial and ventricular rates during exercise.

atrial, right ventricular, and pulmonary artery pressures were normal in the 2 patients without atrial septal defect, and response to exercise during catheterization was determined in these instances (fig. 11). Presence of increased cardiac output, stroke volume, and a widened A-V oxygen difference was confirmed during exercise.

Discussion

The calculation of the working capacity of patients with atrioventricular block with the exercise tolerance test utilized presents some difficulties. In patients without arrhythmias the working capacity corresponds to the submaximal work load, i.e., the load which at a steady state causes a pulse frequency of 170 per minute.[16, 17] It is evident that such rates

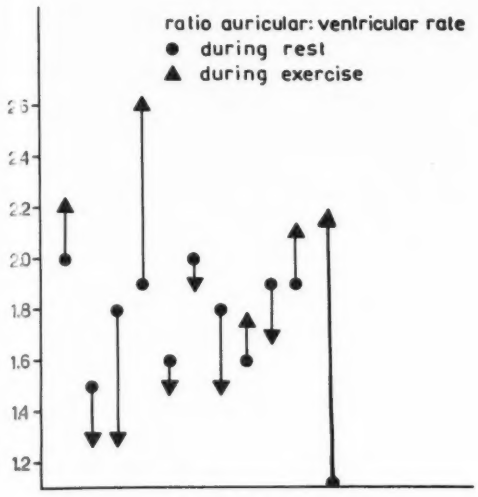

Figure 8

Changes in the ratio of atrial:ventricular rates during exercise.

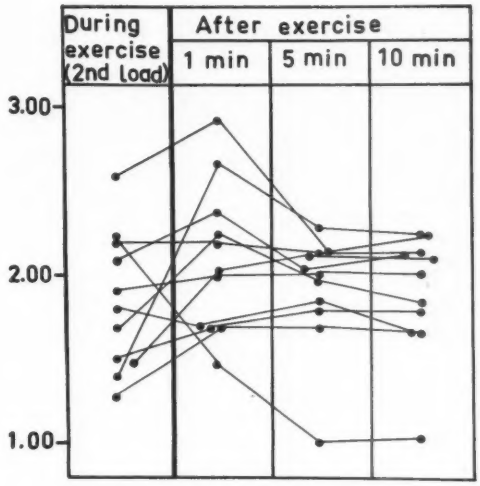

Figure 9

The change in ratio of atrial:ventricular rates during recovery following exercise.

could not be obtained in patients with congenital atrioventricular block. Therefore in the present study the work load that could be tolerated by the patients was taken as the submaximal work load and compared to the one predicted for each case. Holmgren et al.[14] have suggested that the atrial rate instead of the ventricular rate should be used in cases with atrioventricular block. From the results in table 1 it is obvious that the submaximal working capacity as determined above meets the criteria of Holmgren et al. In all patients but 1 (case 2) the atrial rate during the second work load was around 170 per minute (range 160 to 185).

That patients with congenital atrioventricular block have a normal or nearly normal working capacity in a standardized exercise tolerance test demonstrates that this cardiac arrhythmia is not in itself an incapacitating disease, at least in the age range studied. Not only are such patients able to cope with the muscular activity of everyday life without symptoms, but they can also tolerate strenuous muscular exercise. For example, patients 3, 6, 7, and 9 were engaged in usual athletics and patient 4 was an ardent ice-hockey player. Similar isolated examples have been previously reported in the literature.[15, 26]

The ventricular acceleration during exercise observed in these patients with atrioventricular block shows that this circulatory adjustment, which is the most important one during physical effort in normal people, is also of importance in such patients.

The maximal ventricular rate obtained during exercise at submaximal working load showed large individual variations (table 1, fig. 4). Gilchrist[3] studied the effect of a standard exercise tolerance test on the atrial and ventricular rates in patients with acquired complete heart block and found a negative correlation between the atrial and ventricular gains during exercise. He therefore suggested that the Bainbridge reflex was of importance in the large atrial gain with small ventricular acceleration during exercise. Our observations of a positive correlation (fig. 10) are, however, opposite to his. The much larger ventricular accelerations in our patients gave us observations in a different range from Gilchrist's that are not comparable. The difference in myocardial competence between his elderly patients and our young ones may well

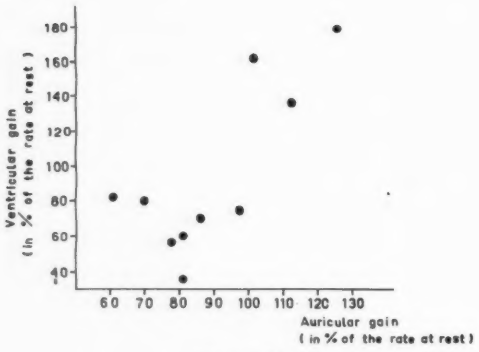

Figure 10

Correlation between increases in atrial and ventricular rates during exercise.

account in large part for the amount of exercise tolerated, in ventricular acceleration, and in the ratios of atrial-ventricular gains.

The factor that determined the maximal ventricular rate was not the rate at rest nor the heart size, since no correlation could be demonstrated between these variables and the maximum ventricular rate (figs. 5 and 6). Furthermore, although the ventricular and atrial rates increased, by and large, in parallel (fig. 4), the agreement between these increases was not complete. The atrial-ventricular ratio showed changes both during transit from rest to exercise and from exercise to rest (fig. 9). These changes were very pronounced in a few cases (fig. 8). The reason for these changes in atrial-ventricular ratio is demonstrated in figure 7. The atrial rate increased in a normal manner, i.e., stepwise, while the increase in the ventricular rate was irregular in the sense that it occurred in many cases either between the rest and the first load or between the first and second load.

Although it might be postulated that the occurrence of ventricular extrasystoles, either isolated or in the form of bigeminy or trigeminy, could be a factor in increasing cardiac output, this does not seem to be the case. Holmgren[14] has demonstrated decreases in mean arterial pressure during periods of bigeminal rhythm. As the increase in ventricular rate produced by exercise is limited in

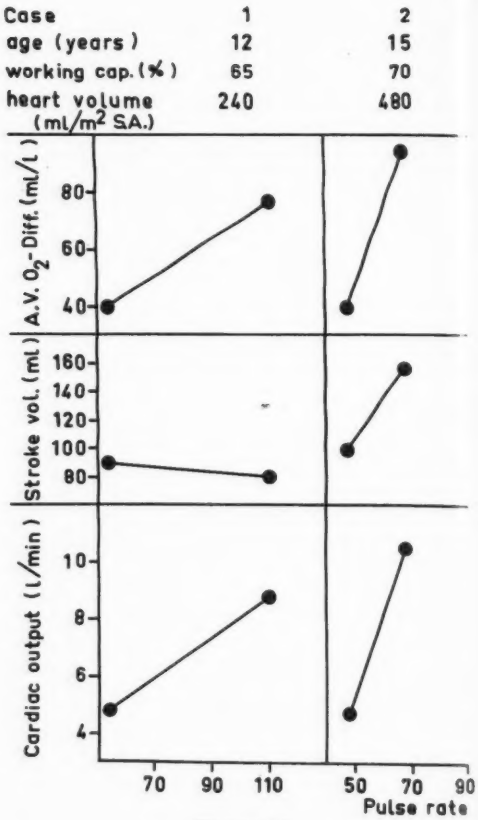

Figure 11

Hemodynamic findings in 2 cases at cardiac catheterization during rest and exercise.

these cases, however, other hemodynamic changes must take place to effect maintenance of a normal exercise tolerance, despite the relative bradycardia. Measurement of the heart size in the present group confirmed previous findings of others that cardiac enlargement is present in atrioventricular block. This increase in heart size permits normal minute volumes by increasing stroke volume[11, 12] and thus aids in supporting a normal or nearly normal working capacity (fig. 1). The importance of cardiac enlargement as a compensatory mechanism in atrioventricular block has even been experimentally demonstrated. Starzl et al.[27, 28] found that dogs with experimentally produced atrioventricular blocks r-

Table 2

Findings at Right Heart Catheterization

Case no.	Pressures in mm. Hg					O_2 saturation (%)	A-V O_2 difference (% Sat.)	Minute volume (liters)	Stroke volume (ml.)	Atrial rate	Ventricular rate	
	RA	RV	PA	BA	Wedge							
5	4	28/3	26/4	80/45	6	97	40	4.8	100	78	48	Rest
							94	10.5	156	158	67	Exercise
7	5	33/6	29/6	110/57	—	99	40	4.8	90	113	54	Rest
							77	8.8	80	166	110	Exercise
8 (ASD)	5	54/9	—	85/35	8	96	33	R 6.3 L 4.5	R 146 L 104	83	43	Rest
10 (ASD)	5	43/6	38/8	95/7 (L. V.)	—	94	40	R 11.0 L 4.5	R 203 L 83	103	54	Rest

gained their preoperative working capacity a few months later when cardiac enlargement and increased stroke volume were obvious.

In 2 patients of our group the hemodynamic adjustments to exercise were observed during cardiac catheterization (fig. 11). The results clearly show the interplay between heart volume, ventricular rate, and stroke volume in such cases. The first case was a 12-year-old girl with normal heart size. The cardiac output during work increased from 4.8 to 8.8 liters per minute by virtue of an increase in ventricular rate from 53 to 110 per minute, the stroke volume remaining practically unchanged. Even the A-V oxygen difference was within the normal range for the changes in heart rate. An increase in cardiac output was also seen in the second patient, a girl of 15 years. But here the increase of minute volume from 4.8 to 10.5 liters per minute was achieved principally through a 50 per cent increase in stroke volume, the ventricular rate increasing only slightly from 48 to 68 per minute. In this case another hemodynamic adjustment was recognized, the A-V oxygen difference increasing above the normal limit to be expected from the normal rate.[29]

Summary

The electrocardiographic and hemodynamic responses to graded exercise in 11 patients with congenital complete atrioventricular block are described. Ventricular rate increases during exercise were unrelated to the resting rate, atrial rate, or heart size. Changes in the ratio of atrial:ventricular rates were observed in all cases during physical work. Physical working capacity was normal or only slightly reduced in all instances. This is accomplished through maintenance of normal minute volumes, which in turn reflects an interplay of several factors: acceleration of ventricular rate, increased heart volume and stroke volume, and a normal or supernormal oxygen-transporting capacity of the blood as reflected in increased amount of total hemoglobin.

Summario in Interlingua

Es describite le responsas electrocardiographic e hemodynamic constatate post graduate exercitio in 11 patientes con congenite complete bloco atrioventricular. Le augmentos del proratas ventricular durante le exercitio revelava nulle correlation con le proratas in reposo, le proratas atrial, o le dimensiones del corde. Alterationes in le proportion inter le proratas atrial e ventricular esseva observate in omne le casos durante le effortio physic. Le capacitate de effortio physic esseva normal o levemente reducite in omne le casos. Isto es le resultato del mantenentia de un normal volumine per minuta, un phenomeno que, de su parte, reflecte un concerto de plure factores, i.e. le acceleration del prorata ventricular, le augmento del volumine cardiac e del volumine per pulso, e un capacitate normal o supernormal de transporto de oxygeno in le sanguine con le resultato de un augmento del quantitate total de hemoglobina.

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The Direction of Blood Flow in Anomalous Left Coronary Artery Arising from the Pulmonary Artery

By DAVID C. SABISTON, JR., M.D., CATHERINE A. NEILL, M.D., AND HELEN B. TAUSSIG, M.D.

MYOCARDIAL infarction in infancy secondary to the anomalous origin of the left coronary artery from the pulmonary artery is now a condition that is being recognized with increasing frequency during life. One of the more interesting aspects of this congenital abnormality is the problem of the direction of the blood flow in the left coronary artery. In 1886 St. John Brooks[1] first postulated that the flow in an anomalous coronary artery was *retrograde*. Following an anatomic dissection in 2 cases in which the right coronary artery arose from the pulmonary artery, he concluded that arterial blood flowed from the normal left coronary artery, which arose from the aorta, through anastomotic collateral vessels into the right coronary artery with ultimate drainage into the pulmonary artery. If the flow is retrograde, it is apparent that one of the coronary arteries is not only failing to supply the myocardium but is actually draining fully oxygenated blood from the heart into the pulmonary artery. Recently Edwards[2] and others have presented further evidence in support of this view. The present communication concerns a patient with anomalous origin of the left coronary artery from the pulmonary artery in whom the direction of blood flow in this vessel was studied and demonstrated conclusively.

Case Report

T. L. (B-65692). This 2½-month-old male infant was referred to the Harriet Lane Home Cardiac Clinic of the Johns Hopkins Hospital on June 3, 1959. He was originally examined at the Memorial Hospital of the University of North Carolina where a diagnosis of an anomalous origin of the left coronary artery from the pulmonary artery had been made by Drs. Herbert Harned and George Summer. The family history was not contributory. The child had a 4-year-old sibling, who was healthy and normal. The mother had noted considerable vomiting toward the end of the pregnancy and her weight gain had been 28 pounds. Delivery was performed by cesarean section 12 days prior to term and an excessive amount of amniotic fluid was noted. The birth weight was 7 pounds 11 ounces. He was a slow feeder from the beginning, and had slightly grunting respirations. An examination at the end of 1 month was said to have been normal. When the infant was approximately 6 weeks of age, he suddenly became quite red in the face and vomited during a feeding and was dyspneic for a short time. Approximately 2 weeks prior to admission he became irritable and shortly thereafter had a deep reddish-blue color of the skin. He was very dyspneic and vomited several times. Shortly thereafter the attending pediatrician noted a heart murmur. Chest films were interpreted as showing cardiomegaly, and the child was referred to the Memorial Hospital of the University of North Carolina. Marked cardiac enlargement was noted, and a grade-I systolic murmur was present along the left sternal border and at the apex. An electrocardiogram showed sinus tachycardia and the pattern of a recent anterior myocardial infarction. A cineangiocardiogram showed the left ventricle to be markedly enlarged, with a very thin wall. There was no evidence of an intracardiac shunt. A diagnosis of anomalous origin of the left coronary artery from the pulmonary artery was made.

On admission to the Johns Hopkins Hospital the infant's weight was 11 pounds, 11 ounces. He appeared well developed and well nourished. He was active, alert, and without cyanosis. The respirations were 44 per minute and had a grunting quality, but there was no marked respiratory distress. The heart was enlarged to the left anterior axillary line and the sounds were somewhat distant. The second aortic and pulmonary sounds were equal. A grade-II, slightly harsh, systolic murmur was heard along the left sternal border and radiated over the precordium. The blood pressure in the right arm by the flush technic was

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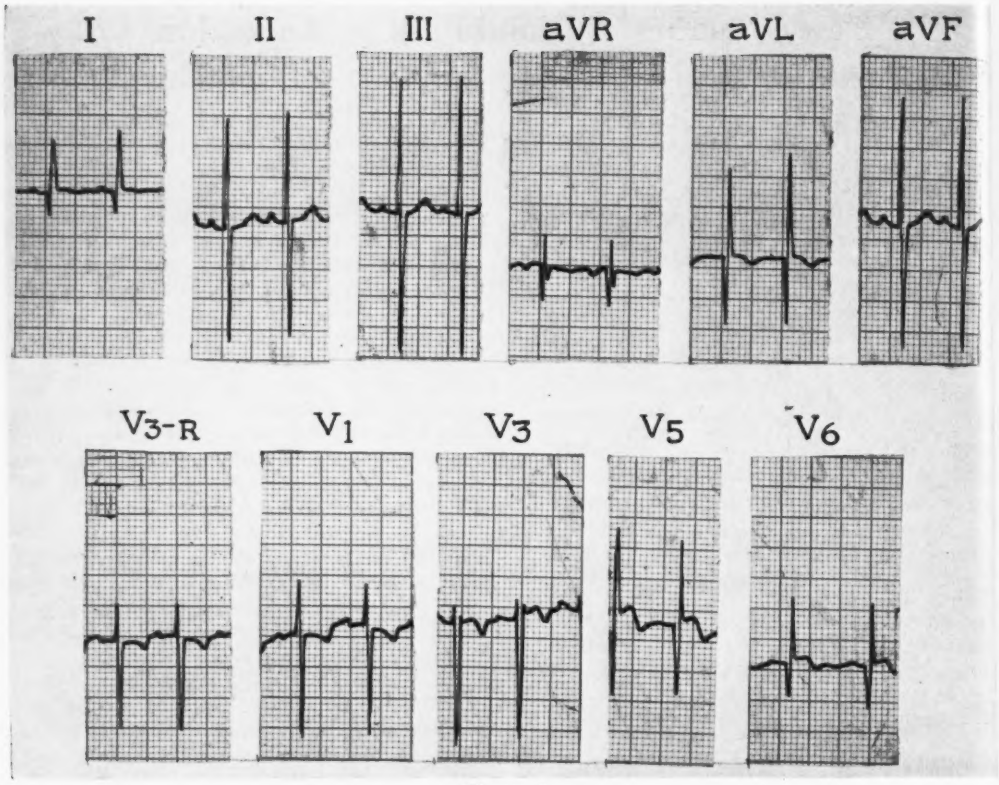


Figure 1

Electrocardiogram at age of 2 months.

90. The femoral pulses were easily palpable. The lungs were clear to percussion and auscultation. The liver was palpable 1.5 cm. below the right costal margin and the spleen was felt 2 cm. below the left costal margin. The remainder of the examination was not remarkable.

Laboratory data: The hematocrit value was 32, the hemoglobin 10.1 Gm. per 100 ml. and the leukocyte count was 13,550 per mm.^{3} An electrocardiogram (fig. 1) showed sinus tachycardia at 140 per minute, left axis deviation, deep Q in leads I, aV_L, V_4, and V_5, elevation of the S-T segments and inverted T waves in V_5 and V_6. The diagnosis was made of recent anterior infarction.

A review of the chest films showed marked cardiomegaly with normal pulmonary vascular markings (fig. 2). The cineangiocardiogram revealed a small right heart with a massively dilated left ventricle. The left ventricular wall was quite thin and pulsations were barely discernible. No evidence of filling of the left coronary artery from the pulmonary artery was seen.

The diagnosis of anomalous origin of the left coronary artery from the pulmonary artery was confirmed and it was decided that operation should be performed. On June 6 the infant was lightly anesthetized with cyclopropane and a left anterior thoracotomy was performed with entrance into the chest through the fourth intercostal space. A considerable amount of fluid escaped from the pericardium. The left ventricle was greatly dilated. A definite myocardial infarct was present on the anterolateral surface of the left ventricle measuring approximately 3 by 4 cm. (fig. 3*A*). With each beat of the heart the area of the infarct bulged paradoxically. A chest retractor was poorly tolerated, producing arrhythmias, bradycardia, and hypotension. It was removed and most of the operative procedure was done without it. The left coronary artery was dissected and was found to arise from the pulmonary artery. It was a vessel of normal size and its anterior descending and circumflex branches were also visualized. The pressure in the left coronary artery was recorded

at 30/15 mm. Hg. An arterial clamp was then applied to the proximal portion of the artery at its origin and the distal pressure was found to be 70 mm. Hg systolic. A simultaneous mean pressure from the pulmonary artery was 25 mm. Hg. A sample of blood from the anomalous left coronary artery was found to have 100 per cent oxygen saturation. At the same time saturation of a sample from the pulmonary artery was 76 per cent. These observations were considered to demonstrate conclusively that the flow in the anomalous coronary artery was retrograde into the pulmonary artery. The anomalous artery was then ligated with 3 suture ligatures (fig. 3*A*) proximal to its division into anterior descending and circumflex branches. At this time the systolic systemic arterial pressure rose from 90 to 120 mm. Hg and it was thought that movement of the left ventricular infaret was less paradoxical. Concentrated phenol was then applied to the entire surface of the heart for deepicardialization. The pericardium was left open and the chest was closed with catheter drainage of the pleural cavity. The patient tolerated the procedure well. An electrocardiogram was recorded continuously during the procedure and no significant or persistent changes occurred. The presumed course of blood flow in the left coronary artery before and after ligation is shown in figure 3*B*.

Following operation the child made an uneventful recovery. The mother noted a marked difference in his appetite and in ability to eat without respiratory distress. Six months after operation his physician reported that he is gaining weight and doing well. A recent electrocardiogram definitely showed less evidence of left ventricular myocardial ischemia, and a chest film showed a slight decrease in the size of the heart.

Figure 2

Preoperative chest film demonstrating marked enlargement of heart, particularly of the left ventricle.

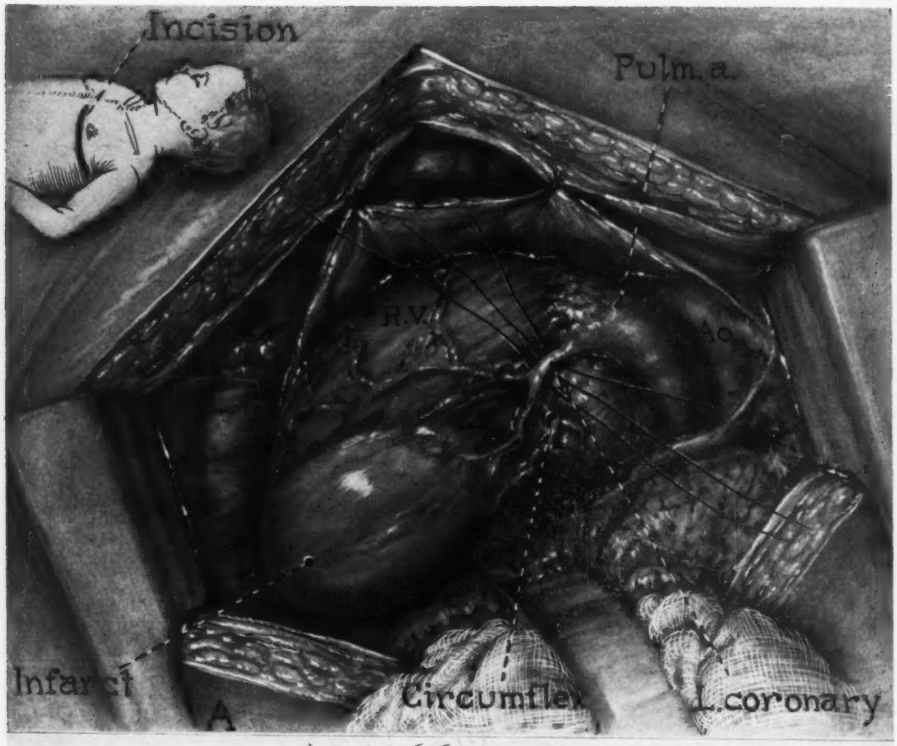
Discussion

In 1911 Abrikossoff[3] first reported anomalous origin of the left coronary artery from the pulmonary artery. Little interest was shown in this condition except for occasional reports until 1933 when Bland, White, and Garland[4] first recorded an electrocardiogram in an infant with this condition and described the clinical and pathologic features. More than 60 cases are now recorded in the literature.

Early diagnosis of anomalous origin of the left coronary artery from the pulmonary artery is essential if successful therapy is to be employed. In many infants with this anomaly myocardial damage may become so extensive that the changes become largely irreversible within a relatively short period. For this reason early recognition and diagnosis is imperative if the most successful results are to be obtained by surgical therapy. The condition should be suspected in an infant having cardiomegaly associated with electrocardiographic evidence of left ventricular infarction. Further confirmation may be obtained by angiocardiography with demonstration of a normal right ventricle and a massively enlarged, thin-walled, left ventricle. It has been noted previously that the anomalous left coronary does not usually fill from the pulmonary artery when contrast media are injected into the right side of the heart, but the normal right coronary artery arising from the aorta may be demonstrated by the performance of a retrograde aortogram.

The seriousness of this anomaly is emphasized by the fact that in untreated cases death secondary to myocardial infarction and cardiac failure usually occurs within the first 5 months. An excellent review of the clinical manifestations and course of infants with this anomaly has been published recently by Keith.[5]

In the past various forms of surgical therapy have been advocated. Gasul and Loeffler[6]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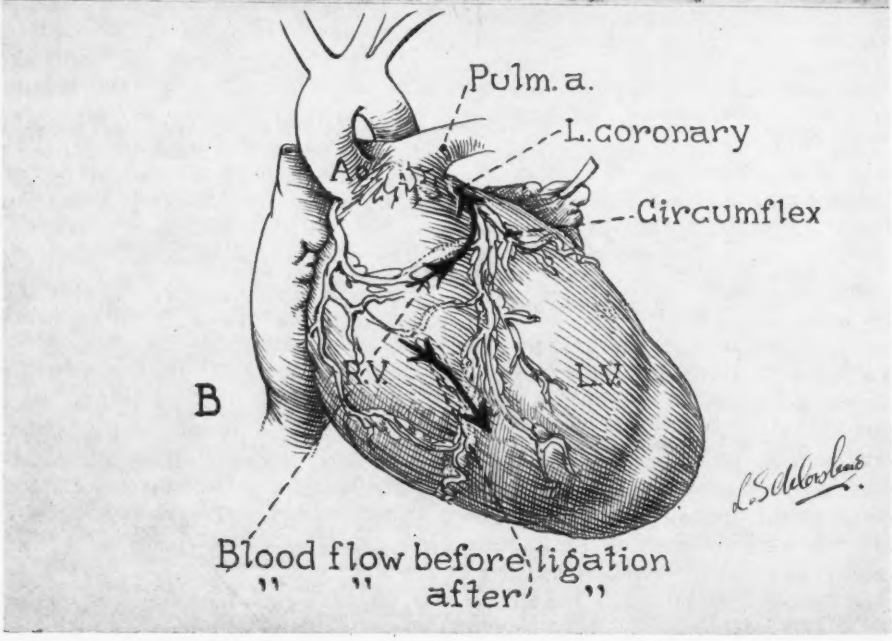
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Blood flow before ligation
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first suggested the creation of an aortic-pulmonary fistula in an effort to increase the arterial pressure and oxygen content of the blood in the pulmonary artery. This was attempted by Potts[7] on two occasions but was unsuccessful. In 1955 Kittle and associates[8] planned a constriction of the pulmonary artery just distal to the origin of the anomalous left coronary artery in an effort to increase the pressure within it, but the infant died while the incision was being made. Others have recognized that the ideal surgical approach to this condition is transplantation of the anomalous coronary artery into a systemic artery by direct anastomosis. Such a procedure is necessarily tedious and difficult, and infants with this condition have an extremely limited myocardial reserve. This procedure was attempted by Mustard[9] in 1953 but the child did not survive. Apley and associates[10] advocated resection of the infarct as a means of reducing the paradoxical motions of the left ventricle as well as ligation of the left coronary artery. Paul and Robbins[11] have employed talc poudrage and recommend its use. In our own experience 2 infants have been treated by chemical de-epicardialization (phenol) in an effort to revascularize the left ventricle. This procedure has appeared to provide real benefit, since both children are surprisingly well 2 and 4 years following operation although cardiomegaly persists.*

Within the past several years there has been increased interest in the direction of blood flow in an anomalous coronary artery arising from the pulmonary artery. In 1886 St. John Brooks[1] reported observations on 2 hearts with this condition, which he found incidentally in the anatomic dissecting laboratory. In both instances the *right* coronary artery arose from the pulmonary artery and his dissections led him to make the following observation: "A consideration of this case will show that a very interesting question is connected with it. Here are two arteries belonging to the different circulations—the pulmonary and the systemic anastomosing with each other. In these circulations, as is well known, the arterial pressure is very much greater in the systemic than in the pulmonary; how then did the blood flow in the anomalous coronary artery? There cannot be doubt that it acted very much after the manner of a vein, and that blood flowed through it towards the pulmonary artery, and from thence into the lungs."[1] Later, Maude Abbott[12] also endorsed this theory of retrograde flow of blood under these circumstances. Recently Edwards[2] has renewed interest in a reconsideration of this problem and has called attention to the fact that infants with congenital cyanotic cardiac disease often have an arterial oxygen saturation which is below that of the venous blood in patients without right-to-left shunts. Yet these patients do not show clinical or pathologic evidence of myocardial ischemia. For this reason he concludes that the reduced perfusion pressure in the anomalous left coronary artery is the most important feature, and has advocated ligation of this vessel as the therapeutic method of choice. This has been performed by Morrow,[13] Jahnke,[14] and others. Edwards[15] offered the following points in support of the theory of *retrograde* flow: "(1) In both normal and anomalous coronary arteries anastomoses exist between the branches; (2) in anomalous origin of the left coronary artery from the pulmonary artery both the right and left coronary arteries have been observed to have been extremely dilated and tortuous in a manner

* These infants will be reported separately as a part of our total experience with this condition.

Figure 3

A. Illustration of heart at operation showing area of infarction and aneurysmal dilation of left ventricle. The left coronary artery was ligated at its origin. B. Direction of blood flow in anomalous coronary artery. Before ligation oxygenated blood from the normal right coronary artery under systemic arterial pressure flowed through collateral vessels into the left coronary with retrograde drainage into the pulmonary artery. After ligation the arterial blood was shunted to the peripheral circulation of the left coronary artery where it could be used by the myocardium.

similar to that occurring in other situations in which arterial venous communications are known to be present; (3) clinical evidence of myocardial ischemia is usually not apparent until several months after birth at a time when the difference between the pressures in the systemic and pulmonary circuits become established; (4) perfusion studies on post-mortem specimens with these anomalous vessels show evidence of large communications between the anomalous and normal coronary arteries; and (5) an observation by Apley and associates that when the coronary artery which arose from the pulmonary trunk was divided at operation bright red blood flowed freely from its distal end."

We have also been able to demonstrate free communication between the left and right coronary arteries in 2 autopsy specimens of the heart from infants with anomalous origin of the left coronary artery from the pulmonary artery. Radiopaque contrast media injected into the right coronary artery completely filled the left coronary artery immediately and actually prior to the filling of the coronary veins. Similarly, methylene blue injected into the right coronary artery quickly filled the left coronary artery and was noted to flow into the pulmonary artery in significant amounts.

In the present case it was possible to isolate the anomalous coronary artery that arose from the pulmonary artery and to measure the pressure within it. This was first done with the vessel open and later with it occluded at its origin. With proximal occlusion of the vessel the pressure rose sharply in the artery, thus suggesting strongly that the source of blood was from the collateral branches. In addition, a sample of blood drawn from the anomalous artery showed full oxygen saturation (100 per cent), whereas a simultaneous sample from the pulmonary artery showed a saturation of 76 per cent. These observations appear to demonstrate conclusively that the blood in an anomalous left coronary artery arising from the pulmonary artery does in fact flow in a retrograde manner. It lends further support to the concept that ligation of the vessel at its origin is a rational method of treatment. This procedure was performed in the infant discussed in the present communication with apparent success.

Summary

An infant with anomalous origin of the left coronary artery from the pulmonary artery is presented, and the problem of the direction of blood flow in the anomalous vessel is discussed. Determinations of arterial pressure and oxygen saturation in the blood of the anomalous artery have demonstrated that the blood in this vessel flowed in a retrograde manner. It is concluded that in this condition oxygenated blood flows from the aorta into the normal right coronary artery and passes through collateral branches into the left coronary artery with ultimate drainage of the blood into the pulmonary artery. Ligation of the anomalous coronary artery with concomitant de-epicardialization appears to be a rational and effective method of therapy. For maximal effectiveness the operation should be performed prior to the onset of irreversible changes, and emphasis is placed upon the importance of early diagnosis and prompt treatment.

Summario in Interlingua

Es presentate le caso de un infante con un arteria sinistro-coronari a origine anormal in le arteria pulmonar. Le problema del direction del fluxo in le vaso anormal es discutite. Determinationes del tension arterial e del saturation de oxygeno in le sanguine del anormal arteria ha servite a demonstrar que le fluxo del sanguine in iste vaso sequeva un direction retrograde. Es concludite que in iste condition sanguine oxygenate flue ab le aorta a in le normal arteria dextero-coronari e passa per brancas collateral a in le arteria sinistro-coronari, resultante ultimemente in un drainage del sanguine a in le arteria pulmonar. Ligation del arteria coronari anormal in concomitantia con dis-epicardialisation pare esser un plausibile e efficace methodo therapeutic. Pro esser maximalmente efficace, le operation deberea esser effectuate ante le declaration de irrevertibile alterationes. Es sublineate le importantia de un precoce diagnose e de un prompte tractamento.

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Sex Differences in the Electrocardiogram

By Ernst Simonson, M.D., Henry Blackburn, Jr., M.D., Thomas C. Puchner, M.D., Pauline Eisenberg, M.D., Fernanda Ribeiro, M.D., and Manuel Meja, M.D.

SEX DIFFERENCES are not considered in contemporary clinical electrocardiographic interpretation. The more commonly used normal standards make no sex differentiation, and some are derived from men alone whereas others are composite data from men and women.[1-4]

There is evidence from earlier studies that sex differences in the electrocardiogram may indeed exist.[5] Small numbers of subjects were analyzed; however, no statistical treatment was provided, and age and relative body weight were not considered in the comparisons.

This study provides data on differences in electrocardiographic characteristics of men and women that may contribute to improved discriminative value of the electrocardiogram in clinical interpretation.

Material and Methods

The 424 men of this study derive from a randomly selected sample of railroad employees, ages 40 through 59 years, from 20 railroad companies operating in midwestern and northwestern United States.* The 142 women, ages 40 through 59, are employees of the Mt. Sinai Hospital, Minneapolis, the Mutual Service Insurance Companies, St. Paul, Minnesota, the Asbury Hospital, Minneapolis, and the Provident Mutual Life Insurance Company, Philadelphia, Pennsylvania. We selected this age range because it is most important in regard to electrocardiographic interpretation of coronary heart disease.

For the experimental groups of "normal healthy" men and women, eliminations from a larger sample were made on the basis of nonelectrocardiographic criteria after medical history and physical examination, urinalysis, and chest x-ray. On the basis of these data subjects were excluded when there was evidence of arterial hypertension (160 mm. Hg systolic or 95 mm. Hg diastolic, or greater), any clinical diagnosis of heart disease, cardiac murmurs greater than grade-II intensity, chronic bronchopulmonary disease, renal disease, diabetes mellitus, thyroid disease, peptic ulcer, active gallbladder disease, or convalescence from recent infections. The groups thus represent clinically screened samples of the American working population, in the age range 40 through 59 years. Relative body weight was calculated from height-weight data for age from the standard Medico-Actuarial tables.[6] This is a rather crude measure but is sufficient for gross characterization of underweight, normal weight, and overweight.

A supine resting 12-lead electrocardiogram (leads I, II, III, aV_R, aV_L, aV_F, V_1-V_6) was recorded on standard direct-writing instruments, at 25 mm. per second paper speed, with 1 mv. = 1 cm. calibration. The measurements were made in duplicate by two investigators. Smoking and hard physical work were proscribed for at least 30 minutes before the recording but prior meal intake was not rigidly controlled.

Results

Statistical analysis revealed no significant differences in electrocardiographic characteristics between partial age groups of 40 to 49 and 50 to 59 years. Therefore, all subjects from 40 to 59 years were pooled with resultant total groups of 424 men and 142 women. The average relative body weight of the men is 102.9 per cent and that of the women 97.4 per cent. Both values for relative body weight are not significantly different from the "normal" (100 per cent). The 5 per cent lower mean relative body weight in the women corresponds to a general trend in regard to the reference data of 1912. Both groups include underweight, normal weight, and overweight persons, but these are similarly distributed in the total groups, and the samples may be considered representative of the general population in regard to relative body weight. Differences in electrocardi-

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*The epidemiologic study of this railroad population is under the direction of Dr. Henry Taylor.

Table 1

Means (M), Standard Deviations (SD) of Amplitudes, Axis, and Intervals in 424 Healthy Men and 142 Healthy Women, Ages 40 through 50 Years

	Men		Women				Men		Women		
Standard Leads	M_1	SD_1	M_2	SD_2	M_1-M_2		M_1	SD_1	M_2	SD_2	M_1-M_2
I_1	0.59	0.23	0.59	0.28	.01	QRS axis	37.2	32.0	40.1	28.8	−2.9
I_2	1.06	0.38	1.02	0.44	.04	ΣQRS	19.8	5.7	20.3	6.4	− .5
I_3	0.23	0.30	0.19	0.31	.04						
II_1	0.25	0.35	0.23	0.42	.01	T_1	1.90	0.75	1.93	0.69	− .03
II_2	0.41	0.83	0.38	0.69	.03	T_2	2.33	0.91	2.25	0.79	.07
						T_3	0.43	0.86	0.36	0.81	.07
III_1	5.97	2.69	6.16	2.70	−.19						
III_2	7.50	3.33	8.09	3.37	−.60	T axis	37.7	20.2	36.9	18.7	.8
III_3	3.21	3.10	3.59	3.19	−.38	ΣT	5.01	1.64	4.91	1.43	.10
S_1	0.70	0.95	0.34	0.59	.35***	*Intervals* (.01 sec.)					
S_2	0.82	1.07	0.67	1.07	.15	P-R	16.7	1.6	15.5	2.0	1.2***
S_3	1.61	2.21	1.40	2.39	.21	QRS	9.0	1.3	6.7	0.9	2.3***

Statistical significance of the mean differences (M_1-M_2) is evaluated by means of the t test (*p = <0.05; **p = <0.01; ***p = <0.0001).

graphic characteristics between the sex groups are therefore not attributable to a different distribution of obese and underweight individuals.

Table 1 shows the means (M) and standard deviations (S. D.) of the amplitudes, axes, and intervals in the standard limb leads of both groups, the mean differences between the groups, and their statistical significance evaluated by the t test. The most significant difference is the shorter P-R and QRS duration in women. The differences in amplitudes are small and statistically not significant except for the slightly larger S wave in lead I in men.

Table 2 shows the comparison of Q, R, S, and T amplitudes in augmented unipolar leads. Since the QRS axis and T axis (table 1) are not significantly different between the groups, subdivision into partial positional groups was not necessary for the comparison of the whole groups. The somewhat higher R wave in aV_F in women corresponds to an average axis deviation to the right, and is statistically significant at the p<0.05 level. The smaller S wave in aV_R and aV_L, and the slightly greater T wave in aV_L were significantly different.

In general, the sex differences in amplitudes found in limb leads are small although some attain statistical significance.

In contrast, figure 1 shows the highly significant differences in precordial leads, with smaller amplitude of R, S, and T waves in the women in all V leads, particularly from V_2 to V_5. The largest difference in R-wave amplitude occurs in V_5 (about 25 per cent larger in men), and in the S wave and T wave in V_3 (about 80 per cent larger in men).

The mean R/S ratio in V_1 is identical in both groups (0.22 in men, 0.21 in women). An analysis of the frequency distribution (in per cent) of the transitional zone is shown in table 3. The transitional zone in men occurs most often in V_3 (31.1 per cent), nearly identical to the frequency for V_3 in women (33.3 per cent). The frequency of the transitional zone to the left of V_3 is significantly higher in men, and to the right of V_3 is significantly higher in women (tested by the chi-square test). The transitional zone from V_4 to V_6 is three times more frequent in men than in women, and to the right of V_3 is two times more frequent in women than in men. Therefore, the transitional zone of women is farther to the right, or counterclockwise.

This was confirmed by an evaluation of the spatial orientation angle in the horizontal plane. Leads are expressed in terms of this angle, with use of the reference system of an earlier communication,[7] in which an angle of

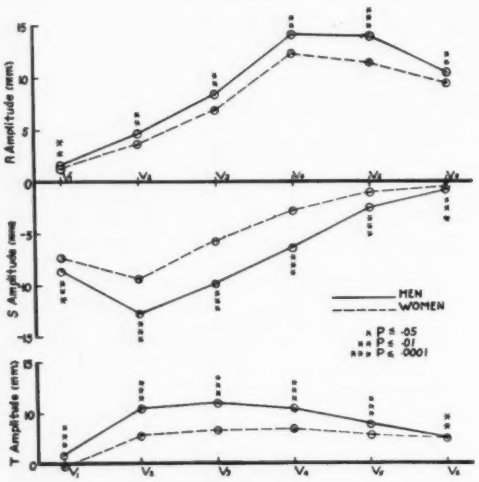

Figure 1

Mean R, S, and T amplitude in V_1 to V_6 in 424 healthy men and 142 healthy women from 40 through 59 years. Statistical significance of the differences is marked by asterisks.

Table 2

Means (M) and Standard Deviations (SD) of Amplitudes in 424 Healthy Men and 142 Healthy Women, Ages 40 through 59 Years

	Augmented Unipolar Limb Leads				
	Men		Women		
	M_1	SD_1	M_2	SD_2	M_1-M_2
Q					
aV_L	0.24	0.34	0.23	0.42	.01
aV_F	0.23	0.35	0.22	0.36	.01
R					
aV_R	0.47	0.63	0.39	0.45	.08
aV_L	3.37	2.50	3.33	2.47	.04
aV_F	4.71	3.26	5.33	3.21	—.63*
S					
aV_R	4.53	3.91	3.59	4.25	.94*
aV_L	1.08	1.51	0.69	1.12	.39**
aV_F	0.87	1.30	0.76	1.43	.11
T					
aV_R	—2.08	0.72	—2.01	0.64	—.07
aV_L	0.88	0.71	1.06	0.67	—.18**
aV_F	1.40	0.81	1.32	0.70	.07

Statistical significance of the mean differences (M_1-M_2) is evaluated by means of the t test (*$p = <0.05$; **$p = <0.01$; ***$p = <0.0001$).

zero points left lateral, and an angle of 90° points directly forward with respect to the anatomic center of the heart. With this technic

Table 3

Distribution of QRS Transitional Zone Expressed in Per Cent for 424 Normal Men and 142 Normal Women, Ages 40 through 59

Location	Men	Women
V_1	1.2	0
V_1-V_2	1.2	4.9
V_2	7.5	9.2
V_2-V_3	11.8	26.8
V_3	31.1	33.1
V_3-V_4	23.8	18.3
V_4	16.0	6.3
V_4-V_5	4.2	0.7
V_5	2.8	0
V_5-V_6	0	0
V_6	0.2	0.7

the mean orientation angle of the transitional zone is 64.3° in women and 59.4° in men. The difference is statistically highly significant, and confirms the results of the distribution analysis (table 3).

However, the transitional zone in the majority of men and women is located from the left of V_2 to position V_4, and extreme clockwise rotation (transitional zone to the left of V_5) or extreme counterclockwise rotation (transitional zone to the right of V_2) is rare in both groups. The sex difference in location of the transitional zone does not account for the large differences in amplitudes of all deflections in chest leads.

Discussion

Major sex differences in electrocardiographic wave amplitudes were found only in precordial leads (horizontal plane), and this was unexpected. The reason is not immediately apparent, though the smaller heart of women, both absolute and in relation to the body weight,[8] may be a contributing factor. In a recent study[9] of the influence of chest configuration in men on the electrocardiogram and the spatial vectorcardiogram, direction rather than magnitude was affected. This makes it less likely that the different sex characteristics of chest configuration account for the smaller electrocardiographic amplitudes found in women. Breast adipose tissue in women would not likely account for the an-

itude differences, since differences are apparent in V_2 at the sternum and V_5-V_6 in the left chest, although this factor cannot be entirely eliminated.

It can be predicted that the magnitudes of the mean and maximal spatial vectors for QRS and T are smaller in women, though no analysis of vector magnitudes was made.

For clinical application it appears that no sex differentiation need be made in regard to *limb*-lead electrocardiographic amplitudes in this age group, but the shorter QRS duration in women, found as well in earlier studies,[10, 11] and the shorter P-R interval, must be considered. This might also be explained by smaller heart size in women. On the other hand, normal limits for *precordial*-lead electrocardiographic amplitudes, largely derived from men, may not be valid for women. Such limits are of more practical value for clinical interpretation than the means and S.D. In these samples, for example, the upper 97.5-per cent limit of R-wave amplitude in V_5 is 21 mm. in women, 25 mm. in men.

Summary

In 424 men and 142 women, clinically "healthy," ages 40 through 59 years, significant sex differences in electrocardiographic characteristics were found. The differences were minor in the limb-lead amplitudes (P, Q, R, S, T), but QRS and P-R duration was significantly shorter in women. Precordial-lead amplitudes (R, S, T) were significantly smaller in women. Present normal standards derived from groups of men are not valid for women.

Acknowledgment

We wish to thank Professor Henry L. Taylor for his cooperation and permission to use the electrocardiograms of the employees of the railroad companies; Dr. James Dahl for providing the electrocardiograms of female employees of the Ashbury Hospital, Minneapolis; Dr. Paul Langner for sending electrocardiograms of female employees of the Provident Mutual Life Insurance Company, Philadelphia, Pennsylvania; Mrs. Jane Bardon and Mr. Andrew Westerhaus for the statistical evaluation; and Mr. Charles Johnson for participation in the measurements.

Summario in Interlingua

In 424 masculos e 142 femininas—omnes clinicamente san e de etates de inter 40 e 59 annos—significative differentias sexual esseva constatate in le characteristicas electrocardiographic. Le differentias esseva minor in le amplitudes del derivationes extremitatal (P, Q, R, S, T), sed le duration de QRS e de P-R esseva definitemente reducite in le feminas. Le amplitudes del derivationes precordial (R, S, T) esseva significativemente plus micre in femininas. Le currentemente usate standards de normalitate derivate ab homines non es valide pro feminas.

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Studies of Peripheral Circulation during Sickle-Cell Crisis

By Felice Manfredi, M.D., Angelo P. Spoto, M.D., Herbert A. Saltzman, M.D., and Herbert O. Sieker, M.D.

IT IS WELL recognized that patients with sickle-cell disease may have a low saturation and tension of arterial blood oxygen. Although arterial anoxemia was first observed in 1942, its exact mechanism is still unknown.[1] It has been shown that the hemoglobin dissociation curve of these patients is shifted to the right, probably because of a decrease in erythrocyte pH.[2, 3] Therefore, a normal level of oxygen saturation would not be possible even in the presence of a normal oxygen tension. A block of diffusion at alveolar-capillary membrane resulting in an increased pressure gradient of alveolar-arterial oxygen has also been suggested as a cause of arterial oxygen unsaturation.[4] It appears more likely, however, that abnormal venous admixture within the lungs, as reported in other anemias,[5] is responsible for a low arterial oxygen tension.[6] Congenital abnormalities in the lung vasculature, opening of pulmonary arteriovenous anastomotic channels, extremely low oxygen tension in the returning venous blood, or pulmonary parenchymal alterations have been suggested as mechanisms by which abnormal venous admixture within the lungs occurs.[6] Apparently, shunting of blood within the lungs accounts for the arterial oxygen unsaturation observed in sickle-cell disease.

The possibility that abnormal shunts are also present in the peripheral circulation of these patients has not been investigated, although it has been recently suggested in the results of experiments intended to show abnormal intrapulmonary venous admixture.[6] The present study was undertaken to investigate the peripheral circulation in patients with sickle-cell disease. In particular, the possibility that peripheral shunting of blood occurs transiently and in relation to episodes of crisis was considered and investigated.

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Methods

Eighteen Negro subjects, ranging in age from 16 to 48 years, were studied in a total of 31 observations. The electrophoretic hemoglobin pattern was SS in 11 patients, SC in 3 patients, and SA in 1. The 3 remaining subjects had hemoglobinopathies, but the exact electrophoretic pattern could not be established because of recent blood transfusions.

Eleven patients were asymptomatic at the time of the study. Repeated observations were made on the other 7 patients during and after sicklemic crises. Abdominal pain, joint symptoms, temperature elevation, leukocytosis, and degree of hemolysis as indicated by changes in hematocrit value, reticulocyte count, and bilirubin level were used to identify a sickle-cell crisis. The extremities and in particular the hands of the patients during crisis were at normal temperature and not flushed or hot.

Indwelling needles were placed in the brachial artery and a superficial forearm vein on the same side. Sufficient time was allowed to obtain a resting state of the subject and to reestablish a free flow in the vein before blood samples were drawn simultaneously in oil-heparin syringes from the artery and the vein. In 2 patients studied during crisis, blood was also obtained by intravenous catheterization at points from the superior vena cava to the superficial vein of the forearm. In 2 patients in crisis, observations were made with and without a venous tourniquet at the wrist, in order to determine the effect of blockage of venous drainage from the hand.

Similar control studies were performed in 6 anemic patients without the sickle-cell trait with a mean hemoglobin concentration of 5.7 Gm. per cent, and in 3 febrile patients with a mean temperature of 38.7 C.

Oxygen content and saturation, pH, and hemoglobin were determined on the paired blood samples. Oxygen and hemoglobin were measured by the spectrophotometric method of Hickam and Frayser.[7] At low hemoglobin concentrations the

oxygen content was determined with a 15 per cent saponin solution instead of the usual 30 per cent. Careful attention was given to the completeness of hemolysis in the blood samples for oxygen determination, since sickle erythrocytes have an increased resistance to hypotonic solutions.[8] Standard Van Slyke determinations for oxygen content and capacity were made for comparison with the results obtained by the spectrophotometric method on 11 different arterial or venous samples. The mean difference between the manometric and the spectrophotometric technics was −0.5 vol. per cent for oxygen content and +0.3 vol. per cent for oxygen capacity. The pH of whole blood was measured with a Cambridge model E pH meter equipped with an enclosed glass electrode. Measurements were made at room temperature and corrected to 37 C. by Rosenthal's factor.[9]

Results

The 11 asymptomatic individuals and the 5 patients studied after resolution of crisis demonstrated a decrease in mean arterial oxygen saturation to 87.9 per cent (table 1, fig. 1). The mean superficial vein oxygen saturation was 66.5 per cent, quite comparable to the value reported by Roddie et al.[10] for oxygen saturation in blood from superficial veins in a group of 15 young healthy subjects. The mean arteriovenous oxygen difference for the group was 2.37 vol. per cent. Fourteen sets of observations were made on 7 patients during sickle-cell crisis, 1 patient (G., J.) being studied during crisis on 5 different occasions. In this group, the arterial oxygen saturation was again found to be low, with a mean of 86.6 per cent. The venous oxygen saturation was constantly high, with a mean of 81.9 per cent. The mean arteriovenous oxygen difference during crisis was 0.47 vol. per cent, and the mean arteriovenous pH difference was only 0.010, in contrast to the value of 0.042 found in the group not in crisis (fig. 1).

Normal arterial and venous oxygen saturations with a mean arteriovenous difference of 2.37 vol. per cent were observed in the control group of 9 patients with anemia or fever (fig. 1).

Patients G., J.; H., J.; and L., B. were studied on 4 to 6 occasions on different days. They were all asymptomatic during at least one study. Figure 2 summarizes the essential data on patients G., J.; and H., J. A small

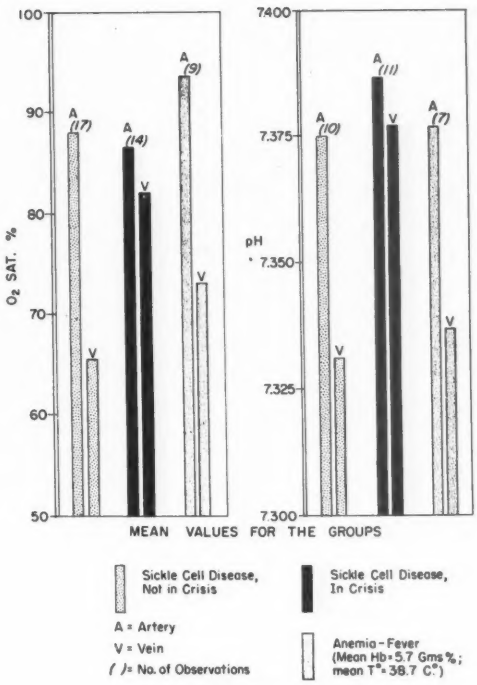

Figure 1

Mean arteriovenous differences for oxygen saturation (left) *and pH* (right) *in a group of asymptomatic patients with sickle-cell disease, in a group during acute crisis, and in a control group with anemia or fever of various etiology.*

arteriovenous difference for oxygen and pH was observed during crisis, and widening of the gradients occurred as symptoms subsided.

When blood samples were obtained from the superior vena cava or deep venous system of the arm, a normal arteriovenous difference was found even during crisis. Figure 3 presents 2 examples of arteriovenous pairs with venous blood drawn from deep and superficial venous circulation at the same time.

In 2 symptomatic patients with small oxygen and pH arteriovenous gradients, the application of a venous cuff above the wrist, which prevented the venous return from the hand, resulted in decreased oxygen and pH blood values in the superficial vein. The arteriovenous gradient for oxygen increased from 0.32 to 3.24 vol. per cent in the first patient, and from 0.44 to 1.31 vol. per cent in the second patient. Concomitantly, the arterio-

Table 1

Data in Eighteen Patients with Sickle-Cell Anemia

Patient No.	Clinical condition	Age	Sex	Hb type	Brachial artery Hb (Gm. %)	Brachial artery O_2 cont. (vol. %)	Brachial artery O_2 sat. (%)	Brachial artery pH	Superficial vein Hb (Gm. %)	Superficial vein O_2 cont. (vol. %)	Superficial vein O_2 sat. (%)	Superficial vein pH	A-V difference O_2 cont. (vol. %)
1. B., Jo.	not in crisis	19	M	SS	9.1	10.3	83.6	—	9.5	9.1	70.2	—	1.2
2. B., W.	not in crisis	19	M	SS	7.4	9.0	89.8	7.367	8.0	5.7	52.5	7.331	3.3
3. G., J. 12-14-58	in crisis	21	M	SS	7.5	9.0	88.7	7.362	7.5	8.9	88.1	7.357	.1
12-17-58	in crisis				7.1	8.4	87.6	7.413	7.0	8.3	87.0	7.389	.1
3-24-59	in crisis				8.3	9.8	89.9	7.377	8.4	9.5	87.1	—	.3
5-8-59	in crisis				5.7	6.7	86.3	7.429	5.8	6.3	80.1	7.421	.4
5-12-59	not in crisis				6.3	7.5	87.4	7.426	6.3	4.5	52.6	7.345	3.0
5-23-59	in crisis				7.7	8.6	79.9	7.393	8.2	8.3	77.0	7.383	.3
4. H., J. 12-26-58	in crisis	27	M	SC	12.4	16.9	98.3	7.465	12.1	16.1	93.0	7.460	.8
7-24-59	in crisis				12.0	15.2	93.2	7.318	11.9	13.5	83.0	7.306	1.7
7-25-59	in crisis				11.4	13.8	88.7	7.359	11.5	13.8	88.2	7.348	0
7-27-59	not in crisis				12.3	15.8	93.9	7.313	12.3	11.4	58.0	7.290	4.4
5. H., B.	in crisis	19	M	—	9.3	11.9	96.2	7.419	9.6	11.5	87.7	7.394	.4
6. I., W.	in crisis	32	M	SC	11.0	12.8	85.3	—	11.0	11.6	76.8	—	1.2
7. L., B. 5-25-59	in crisis	30	F	SS	7.0	7.6	75.9	7.336	7.0	6.7	67.1	7.336	.9
5-28-59	not in crisis				7.6	8.7	84.3	7.400	7.3	5.9	59.8	7.394	2.8
6-20-59	in crisis				8.1	9.6	82.7	—	8.0	9.6	77.1	—	0
7-6-59	not in crisis				8.9	11.2	91.8	—	8.9	8.9	67.7	—	2.3
8. M., M.	not in crisis	17	F	SS	8.9	10.4	85.9	7.377	9.5	8.4	64.5	7.313	2.0
9. M., J.	not in crisis	48	M	SA	11.8	14.6	91.0	7.374	12.0	13.1	80.2	7.347	1.5
10. M., R.	not in crisis	46	M	—	7.8	7.8	74.0	7.405	8.1	6.4	60.3	7.293	1.4
11. N., A. 10-15-58	in crisis	30	M	SS	5.0	4.8	70.6	—	5.0	4.8	70.6	—	0
10-16-58	not in crisis				6.0	7.8	95.2	7.190	6.0	6.7	81.4	7.154	1.1
12. N., E.	not in crisis	16	F	SC	8.1	9.9	89.9	7.360	8.1	6.6	60.4	7.312	3.3
13. P., L.	not in crisis	18	F	SS	8.1	10.1	91.3	7.359	7.7	6.7	64.4	7.335	3.4
14. S., J.	not in crisis	34	M	SS	10.6	12.5	86.0	—	10.1	10.6	77.7	—	1.9
15. S., A.	not in crisis	36	M	SS	11.1	13.6	90.0	7.372	11.1	10.8	71.4	7.357	2.8
16. W., R. 2-7-59	in crisis	25	F	SS	6.9	8.4	89.0	—	6.9	8.0	85.0	—	.4
2-9-59	not in crisis				6.9	8.1	86.5	—	7.0	6.9	72.4	—	1.2
17. W., W.	not in crisis	30	M	—	7.9	9.1	84.7	—	8.0	5.9	53.8	—	3.2
18. W., Y.	not in crisis	20	F	SS	7.2	8.9	90.4	—	7.2	7.3	74.2	—	1.6

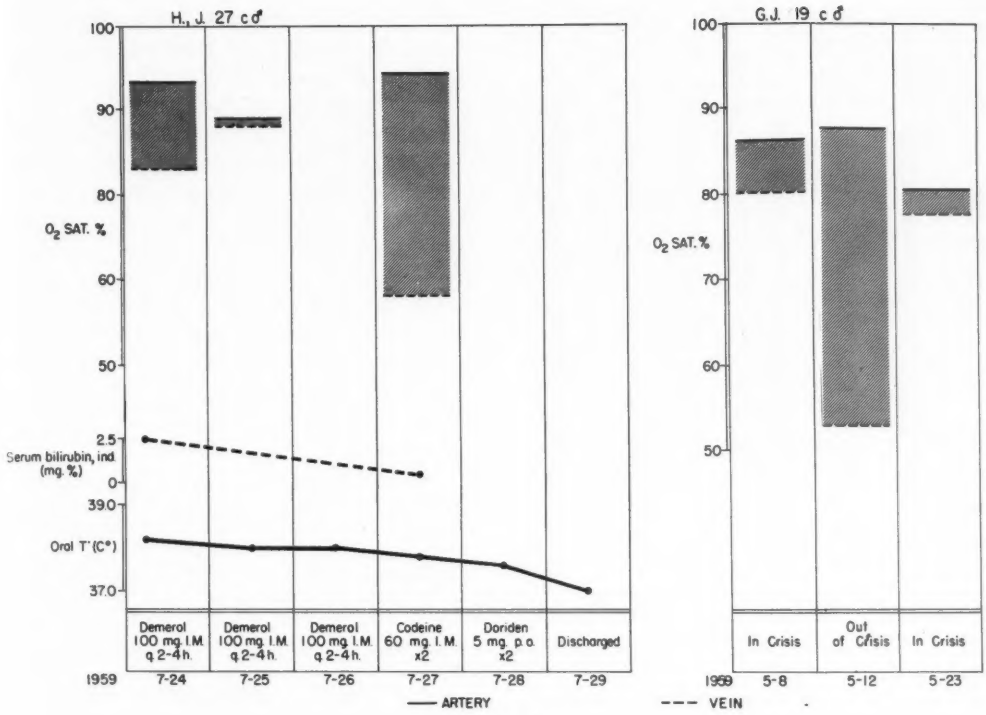

Figure 2

Arteriovenous oxygen differences and clinical course of 2 patients with sickle-cell disease.

venous gradient for pH increased from 0.004 to 0.018 and from 0.002 to 0.008 in the 2 subjects.

Discussion

This study indicates that during sickle-cell crisis arterialized blood is present in the superficial veins of the forearm, as evidenced by the oxygen content and pH values. In all the determinations on patients with sickle-cell disease who were not in crisis and in the control patients who were febrile or anemic, wide arteriovenous differences for oxygen and pH were observed. The narrow arteriovenous difference during crisis suggests an increase in blood flow or a decrease in oxygen uptake by the tissue.

Fever or anemia, or both, during crisis could account for arterialization of venous blood on the basis of an increase in peripheral blood flow. However, the 9 patients without sickle-cell disease but with fever or profound anemia showed a normally wide arteriovenous difference for oxygen. Furthermore, the appearance of the extremities of these patients in crisis did not suggest dilated vasculature or increased blood flow.

It is possible that the arterialization of venous blood may be due to decreased oxygen utilization by the tissues during crisis. However, in a group of 13 patients with sickle-cell anemia, Leight et al.[11] found an increase in per cent oxygen utilization by the tissues. In view of the lack of correlation between the increase in cardiac index and the decrease in hemoglobin level, they postulated the existence of a peripheral compensatory mechanism whereby the per cent of oxygen extraction in the tissues is increased as the oxygen content of arterial blood is lowered. Since most of our patients had arterial oxygen unsaturation, Leight's observation would suggest a low oxygen content in the returning superficial ve-

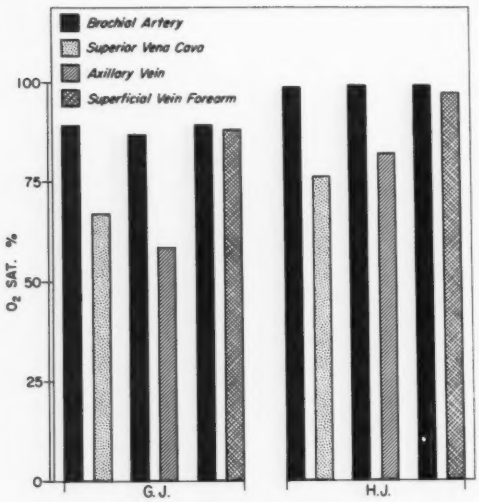

Figure 3

Oxygen gradient between arterial and deep venous system (superior vena cava and axillary vein), and between arterial and superficial venous system (superficial vein of the forearm) in 2 patients with sickle-cell disease during an acute crisis.

nous blood. It must be emphasized that the patients reported by Leight were not studied during acute crisis. Moreover, it is possible that the increased oxygen utilization by the tissues demonstrated by these investigators occurred in the deep muscles and not in the cutaneous areas, since in their study the arteriovenous differences referred to mixed venous blood samples from the pulmonary artery.

It may be postulated that arterialization of superficial venous blood during sickle-cell crisis results from arteriovenous shunts in the superficial tissues of the hands. Arteriovenous anastomoses of considerable size have been demonstrated anatomically in the skin.[12] Moreover, even in the absence of anatomically distinct shunts, the blood may bypass the major portion of the capillary network where oxygen is removed by the tissues. Neuroregulatory mechanisms may control the flow of blood through the various pathways.[13, 14] It is well recognized that both vasodilator and vasoconstrictor nerves have a part in regulating the circulation through the skin of the forearm.[15] In sickle-cell disease, Kimmelstie observed ischemic necrosis without vascula thrombosis in various organs including th lungs.[16] He postulated that a neurogeni mechanism affecting the capillaries is the fa tor initiating sickle-cell crisis. This neur genic mechanism could be responsible for d verting arterial blood to the cutaneous vein through anatomic or functional bypasses, s that oxygen could not be removed by the ti sues. The widening of the arteriovenous di ference when a venous tourniquet was place at the wrist or when samples were drawn fro the deep venous system via catheterizatio indicates that only the superficial vasculatur is involved in this phenomenon.

Regardless of the mechanism involved, th correlation between a narrow arteriovenous difference and sickle-cell crisis appears to b consistent. It is suggested that the finding o arterialized venous blood in patients with sickle-cell anemia is an additional aid in the differential diagnosis of sicklemic crisis.

Summary

In 18 Negro patients with sickle-cell anemia or sickle cell-hemoglobin C disease, gradients of oxygen and pH were measured between brachial artery and superficial and deep venous system of the upper extremity. The results obtained during crisis were compared with those obtained from asymptomatic patients.

Arterial oxygen unsaturation, with normal arteriovenous gradients for oxygen and pH was observed in the 11 asymptomatic patients. Unusually low arteriovenous gradients for oxygen and pH, mainly due to abnormal venous values, were found when blood draining from cutaneous areas was compared with arterial samples in the 7 patients studied during acute crisis. The 5 patients restudied after symptoms subsided showed a return toward normal of arteriovenous differences.

The evidence suggests that during crisis arterialization of venous blood is the result of anatomic or functional bypasses in the superficial circulation, so that oxygen is not removed by the tissues. It is postulated that a

vascular neurogenic mechanism may be the precipitating factor in sickle-cell crisis.

It is also suggested that a low arteriovenous oxygen gradient or arterialization of superficial vein blood may be used as a laboratory aid in establishing the diagnosis of sickle-cell crisis in uncertain cases.

Summario in Interlingua

In 18 patientes negre con anemia a cellulas falciforme o morbo drepanocytic a hemoglobina C, le gradientes del oxygeno e del pH esseva determinate inter le arteria brachial e le systema venose superficial e profunde in le extremitates superior. Le resultatos obtenite ab patientes in stato de crise esseva comparate con illos ab patientes asymptomatic.

Dissaturation oxygenic arterial in le presentia de normal gradientes arterio-venose pro oxygeno e pH esseva observate in le 11 patientes asymptomatic. Inusualmente basse gradientes arterio-venose pro oxygeno e pH, principalmente in consequentia de anormal valores venose, esseva trovate in comparationes de sanguine drainate ab areas cutanee con specimens arterial in le 7 patientes studiate in stato de crise acute. Le 5 patientes qui esseva restudiate post que le symptomas subsideva monstrava un retorno verso le norma con respecto al differentias arterio-venose.

Le observationes pare indicar que durante le crise un arterialisation de sanguine venose es causate per detornos anatomic o functional in le circulation superficial, de maniera que le oxygeno non es acceptate per le tissus. Es postulate le possibilitate que un mechanismo vascular neurogenic es le factor precipitante in le crise drepanocytic.

Es etiam suggerite que le constatation de un basse gradiente arterio-venose de oxygeno o de arterialisation del sanguine venose superficial pote esser usate como adjuta laboratorial in establir le diagnose de crise drepanocytic in casos dubitose.

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SYMPOSIUM ON CORONARY HEART DISEASE

The Use of Anticoagulants in Coronary Heart Disease

Progress and Problems: 1960

By IRVING S. WRIGHT, M.D.

WHILE anticoagulants in the treatment of coronary heart disease are now widely accepted throughout the civilized world and they are used daily in the treatment of many thousands of patients, some problems relating to their use still remain to be resolved. The purpose of this paper is to review some of these problems and to suggest methods by which they may be met. It is not necessary to present new evidence for the use of anticoagulants in the treatment of myocardial infarction. The original findings of the Committee on Anticoagulants of the American Heart Association[1] have been confirmed by workers in many countries on both sides of the Iron Curtain. Cardiologists and internists as well as many well-trained general practitioners carry out anticoagulant therapy satisfactorily. Treatment is easier with the patient in a hospital, but is possible while the patient is home provided accurate laboratory facilities are readily available. The question whether it is desirable to give all patients with acute myocardial infarctions anticoagulant therapy is one that each physician must decide for himself. Most leading cardiologists state that they are unable to differentiate during the early stages of an attack between patients who will continue as "good risk" and those who will become "bad risk" patients. The result of not administering anticoagulants to some of the so-called "good risk" cases has too often been the development of severe complications of a thromboembolic nature.[2] Under most circumstances anticoagulants are given if clinical and laboratory facilities are readily available.

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The Technic of Therapy

There are many anticoagulants available for use by the physician. Heparin still remains the choice when rapid anticoagulant action is desired. Usually it is given in dosages of 75 to 100 mg. intravenously or subcutaneously. (U.S.P. XVI minimum potency is proposed as 120 units per mg.) Intravenous action is somewhat more rapid but results in a brief but marked prolongation of the clotting time with restoration to normal within 4 to 8 hours or less. Subcutaneous or intramuscular injections of heparin are now widely used in dosages of 75 to 100 mg. given at intervals of 8 to 12 hours, depending on the clotting time. In some areas heparin is used throughout the acute stages of the attack. The Lee-White clotting time, although a crude test, still remains the choice for the control of heparin administration. It is desirable that the clotting time, which may increase to 3 or 4 times the control level, return to approximately twice the control time just prior to the next injection. For example, if the clotting time by the test performed is normally 8 minutes, a test performed prior to the next injection should not be shorter than approximately 16 minutes. If it is shorter, it indicates that the time space between the 2 injections should be decreased or the dosage increased. If it is much longer than twice normal, the time spacing should be spread in an effort to avoid overdosage. Many physicians now give from 1 to 4 doses of heparin during the initial period of ant-

coagulant therapy for myocardial infarction. There is, however, little valid evidence that this is necessary in patients who are not obviously very ill at the time. Given at intervals of 24 hours or more, it has not proved successful. The long-acting preparations of heparin are used less frequently than formerly. Sublingual or oral administration of heparin is of no value for anticoagulation.

Coumadin (Warfarin sodium, Liquamar (phenprocoumon), Dicumarol (bishydroxycoumarin), or phenylindanedione are usually started at the same time the heparin is begun. All these anticoagulants and other equally effective derivatives of similar compounds are now in common use. They should be administered in an initial large dose. The second day the patient should receive approximately one half the starting dose and thereafter the dose that is considered to be average for the drug. By this time the prothrombin time will be found to be prolonged; with daily determinations of prothrombin times, it is possible to establish a stabilizing dose. The most satisfactory initial dose of coumadin is between 35 and 45 mg. daily, and the second dose 15 to 20 mg. Beginning with the third day the patient receives 5 to 10 mg. daily. For Liquamar the initial dose is usually 15 to 21 mg., the second dose 9 to 12 mg., and the daily dose thereafter 3 or 6 mg. When the effect of the prothrombin time is considered to be at therapeutic levels, heparin is discontinued. A satisfactory prothrombin time should be between 1½ and 2 times the normal control prothrombin time. For example, if the control prothrombin time is 15 seconds, the treatment level should be between 22.5 and 30 seconds, preferably dividing this figure about in half (26 or 27 seconds).

The contraindications have been reported many times, and must be well understood by all who prescribe anticoagulants. Occasionally the physician is confronted with the fact that his patient has had a duodenal ulcer and may even have suffered a hemorrhagic episode in the past. This presents a calculated hazard, but it is usually more likely that the patient will die or suffer severe complications from his myocardial infarction than from the duodenal ulcer, which may have been relatively quiescent for months or even years. Under such circumstances, antacid or neutralizing preparations are administered and the patient receives an ulcer diet. He is carefully watched for evidence of bleeding, but otherwise anticoagulant therapy is carried on in the usual manner. Many other examples might be given in which special care is essential.

The Value of Long-Term Anticoagulant Therapy

Once the value of the administration of anticoagulants during the first month after an acute myocardial infarction was well established, the question arose as to how long anticoagulant therapy should be continued. Series of cases were compiled to evaluate the effect of continued treatment on the complications or on the longevity of patients who had suffered one or more myocardial infarctions. Many reports have appeared, notably by Nichol,[3] Borg, Keyes, Drake, and Smith[4] Tulloch,[5] Askey,[6] Waaler,[7] Suzman,[8] Owren,[9] and Manchester.[10] These studies have been developed in a variety of ways, and some have justifiably been criticized from a strictly statistical viewpoint. The consistency of their results could not be ignored, however, and as the results accumulated they presented fairly strong evidence in favor of long-term anticoagulant therapy. Friedberg[11] recently compiled a table that included in summary the sum of 2,253 control cases and 735 treated cases. The mortality for the treated cases was consistently reduced to between one third and one quarter of that of the control cases and the recurrences of myocardial infarction to between one quarter and one sixth of the control cases.

One of the more comprehensive studies was that reported by Bjerkelund[12] of Oslo, Norway, in a comprehensive monograph based on experience with 251 patients in a well-controlled clinical trial. With patients under 60 years old on long-term treatment with Dicumarol, he found a statistically significant reduction both in the incidence of recurrent infarction and in the mortality during the first 12 months after an acute infarct. The

incidence of recurrent infarction and mortality in patients over 60 years of age during the first 12 months was also considerably lower in the treated than in the control group, but the difference was not statistically significant. Attacks of severe retrosternal pain in which the presence of recurrent infarction was suspected but not verified were observed about half as frequently in the treated group as in the control group. The morbidity from cardiovascular disease judged by the frequency and duration of admission to hospitals during the observation period was considerably lower in the treated than in the control group. Severe heart failure developed less often in the treated than in the untreated group. The electrocardiogram returned to normal more often after the recorded infarct in the treated than in the control group. The evidence of thrombosis in the coronary arteries shown at autopsy was significantly lower in the treated than in the control group. In his investigation as a whole, treatment during the observation period resulted in a reduction of the incidence of recurrent infarction by about 45 per cent and in the mortality from cardiovascular diseases by about 37 per cent. Because of the less striking effects of anticoagulants after the first 12 months, he raised the question whether it would not be advisable to consider discontinuing therapy at the end of 12 months. Our experience[13] and also that of Owren,[14] however, has demonstrated a rather sharp increase in thromboembolic complications following cessation of treatment; therefore, this should be undertaken with considerable hesitancy and caution. This position has been recently confirmed in a report by Sise and his co-workers.[15]

The most recent comprehensive study of this nature was published in a report of the working party of the British Medical Research Council entitled "An Assessment of Long-Term Anticoagulant Administration after Cardiac Infarction."[16] This Committee was headed by Sir George Pickering and was made up of outstanding cardiologists. It functioned under the critical statistical guidance of Dr. D. D. Reid of the London School of Tropical Medicine. Cases were studied in 15 of the leading medical institutions of Great Britain. The purpose of the investigation was to determine whether long-term anticoagulant therapy following myocardial infarction is worthwhile. This report is commended to the reader for detailed study. The analysis was based on experience with 383 patients who had recovered from the acute phase of a cardiac infarction of defined severity and who were thereafter divided in an unbiased selection into "high dosage" or "treated" and "low dosage" or "untreated" groups. Actually the "low dosage" or "untreated" group did receive one milligram of phenindione per day, a token dose that had no measurable effect on the coagulation of the blood. The "high dosage" group received the amount of phenindione necessary to affect the clotting mechanism properly for therapeutic purposes. The conclusions at the end of 2 years were as follows:

1. Although the death rate was higher in the low dosage series there is just the possibility that the difference could have occurred by chance. No difference was apparent in females but the numbers were too small to exclude such a difference.

Actually the death rate decreased one third in men, from 18 to 10 per cent. This is approximately of the same order as the decrease in the death rate during the first month of therapy originally reported by the Committee on Anticoagulants of the American Heart Association,[1] and it also corresponds with the decrease in death rate of one third following the use of anticoagulants for thrombotic strokes as reported by Groch, McDevitt, and others from our laboratory.[17] Thus, it seems that the thrombotic tendency in both these conditions produces about one third of the subsequent deaths and that if this is successfully prevented, one can anticipate a mortality decrease in approximately that amount.

2. When the infarcts serious enough to cause permanent withdrawal from the trial were added to deaths as a combined index from prophylactic failure, there was a significant reduction in their frequency among the males receiving high dosages and there was a suggestion of better result in males under the age 55.

3. The same trends appear even more clearly

when the total reinfarction rate is used as a basis of comparison. Under the age of 55 males on high dosage suffered recurrent infarction at only one-fifth of the rate of those on low dosages. These differences are statistically significant.

4. The proportionate reduction in the risk of reinfarction achieved by the high dose regimen is slightly greater among patients with a previous history of one or more infarcts, but the difference is not statistically significant.

5. The difference in the death rate is most evident in the first six months of the follow-up period, but the disparity and the reinfarction rate is maintained for at least two years in the follow-up period.

Two years was the duration of the study up to the time of the report, so that information regarding what may have happened after that was not included.

6. More men given the higher dosage returned to work during the period and they were more often free from angina.

7. There were 15 withdrawals from the high dosage series because of the onset of conditions actively or potentially associated with hemorrhage. Four major cerebral vascular accidents, three causing withdrawal and one death were reported among the high dosage series. Only one patient on low dosage suffered a cerebral hemorrhage, but embolism was a major complicating feature in the terminal illness of three of them. There were 48 minor hemorrhagic incidents in the high dosage group compared with eight among those on low dosage.

These studies have been compared with studies previously reported and were found in close agreement in many respects. As has been pointed out, there is an apparent decrease in the benefits after the first year although benefits are measurable in subsequent years. This has not been reported in all series, but there is an explanation for its occurrence and it may be expected. A certain selection takes place as more of the control cases die. The anticoagulant therapy keeps alive an increasing number of what might be termed "border-line" patients. The "control" group gradually loses these by death, and, therefore, is made up of patients who might be considered those with the best natural prognosis. The "treated" group accumulates the corresponding patients by keeping them alive and, therefore, the series becomes increasingly weighted against the "treated" group. These patients will begin to die at a later date as their atherosclerosis progresses and from other complications, but it is well worthwhile to keep them alive for 2 to 5 years or longer if possible, as it now seems to be. One may conclude that the value of long-term anticoagulant therapy following myocardial infarction is now reasonably well established.

The main challenge that confronts us at present is the provision of such service to patients on a large scale. This is a matter of considerable concern to all, but especially to the British Medical Research Council because of the responsibility to provide care under the National Health Act. It does raise a serious question about the number of patients who might be expected to benefit and therefore to require this form of treatment. A. S. Douglas,[18] Secretary of the Working Party Committee, has reported a survey of patients who might require or be deserving of anticoagulant therapy. Strictly on the basis of coronary artery disease and without consideration for the other indications for long-term anticoagulant therapy, it was determined that 1 per 380 of the population, including all from infancy to old age, had suffered an infarction within the previous 2 years and was still alive, and an additional 1 per 170 was suffering from angina. One in a hundred of the population might be a candidate for long-term anticoagulant therapy. If only the population over 40 years of age was considered, the number of candidates was 1 in every 35 of the population. Based on these figures, he concluded, that there were in the population in the west of Scotland, about 30,000 patients to be treated. Similar figures were developed for Scotland, England, and Wales, which amounted to approximately 500,000 persons. On the basis of cost it was estimated that this would amount to something in the neighborhood of 6 million pounds during the first year. In terms of American currency, this would be $16,800,000. If this were to be thought of in terms of the United States, it would be necessary to include consideration of the vastly greater population and also the

greater distances involved. In addition, in neither country are there sufficient technicians, well-trained physicians, or laboratory facilities available to carry out such a program. These figures do not have complete validity, since many of the patients because of contraindications, inconvenience, tempermental unsuitability, and other reasons could not be introduced into such a program. Nevertheless, the magnitude of the problem and the need for planning for the future become obvious. This should be of increasing interest not only to practicing physicians but also to public health officials, since the public health services could well play a leading role in providing better standardization of laboratory tests and in the training of technicians. It is a major challenge to the medical-school faculties. No longer should physicians be graduated without a sound understanding of the basic principles of anticoagulant therapy.

Anticoagulants in the Treatment of Angina

Another facet of this interesting problem is the question whether patients should be given anticoagulant therapy who are suffering from angina without having had definite evidence of myocardial infarction. This will be made the subject of additional study by the Working Party Committee. Reports by Owren,[19] Beamish,[20] Nichol,[21] and others indicate that the death rate of patients on anticoagulant therapy because of angina due to coronary artery disease is approximately one half of those not on anticoagulant therapy over a period of years of observation. This possibility is certainly worthy of further careful study, since true angina is undoubtedly of serious importance to very large numbers of patients. The Working Party of the Medical Research Council is interested in such a study. However, the determination of criteria for angina due to coronary artery disease is fraught with considerable difficulty and in itself will constitute an engaging study.

The Use of Anticoagulants during Surgical Procedures

A question that frequently arises in the course of long-term anticoagulant therapy is whether it is safe or advisable to proceed with surgery while the patient is on anticoagulant therapy, or whether it is necessary to discontinue the anticoagulant prior to the surgical intervention. This has become more sharply focused by the reports of Carter and others[13] from our laboratory and also of Sise[15] and his co-workers from Boston, which indicate that cessation of anticoagulants is associated with increased risk of thromboembolism. We have seen several patients who, when anticoagulants were discontinued for such minor procedures as tooth extraction, developed serious complications such as permanent hemiplegia within a few days. Therefore, one should not discontinue anticoagulants in patients who have previously shown a definite thromboembolic tendency without good and sufficient reason. The reason for this increase in thromboembolic episodes, especially during the first 6 weeks to 3 months after discontinuing anticoagulants, is not fully understood. It has been rather loosely termed a "rebound phenomenon," suggesting that following cessation there is actually an increase in the tendency to thrombosis of the blood. This has been difficult to substantiate by means of careful laboratory tests for many clotting factors. Another factor may play a leading role.

While the long-term anticoagulant therapy does decrease the frequency of thromboembolic complications, it is not believed that it affects the progression of the deposition of cholesterol and lipid plaques in the pathogenesis of atherosclerosis. Therefore, with the passage of time more and more narrowed arterial channels develop. These would, in the normal course of events, be subject to early thrombotic closure, but when the blood is under the influence of anticoagulants, these narrowed and often roughened surfaces do present areas in which clotting may take place easily. Thus, instead of a "rebound phenomenon," one might more correctly consider this as a "catching-up process," in other words, a process by which the natural course of the combination of atherosclerosis and thromboembolism which has been delayed by anticoagulants catches up to the status that would

ave been reached if they had not been used.

It has now been clearly demonstrated that major surgery can be conducted successfully with the patient on anticoagulant therapy. Storm and Hansen[22] have reported series of patients who have had major cardiac and pulmonary surgery, even lobectomy. I had the pleasure of seeing the first 2 patients in whom Storm had performed aortic graft replacements while they were on active anticoagulant therapy. In this country, Miscall has now compiled a series of over 100 patients on whom he has performed mitral commissurotomy while they were on anticoagulant therapy. While there has been some increase in bleeding, there has been a markd decrease in the incidence of thromboembolic complications following this procedure as compared with a controlled series. It is not the purpose of this paper to evaluate the importance of this type of surgery, but rather to point out that its feasibility has now been demonstrated if the surgeon uses proper and more complete hemostatic technics. Certainly this experience suggests that one may be justified in maintaining patients on anticoagulant therapy during minor surgical procedures. We do not discontinue anticoagulants for the extraction of teeth at the New York Hospital at present. Dr. Behrman has compiled a series of more than 75 patients on anticoagulant therapy from whom he has extracted teeth without any difficulty whatsoever. These have included extractions of simple uncomplicated molar extractions, 6 teeth from 1 patient, molars with abscesses, and in 1 case 4 teeth were removed with bone trimming. Our general plan is to have the prothrombin time approximately 1½ the normal control for such procedures. While the use of this technic for major surgery is still being evaluated more completely, the risk of discontinuing anticoagulant therapy may force the issue and result in more patients being operated on during it.

Relationship of Drugs to Anticoagulant Therapy

It has been repeatedly emphasized that the administration of large amounts of salicylates to the patient on anticoagulant therapy may greatly prolong the prothrombin time and occasionally lead to hemorrhage. The chemical relation of salicylates to the coumarin compounds may augment their action on the prothrombin complex. In addition, the use of certain of the gut-sterilizing antibiotics such as chloramphenicol, chlortetracyclene hydrochloric acid, and some of the urinary antiseptics such as sulfasoxazole and nitrofurantain may result in marked changes in the prothrombin time. It is believed that these drugs may interfere with the production of vitamin K by changing the bacterial flora of the gastrointestinal tract. This needs further study. However, when these or other drugs are administered to the patient on long-term anticoagulant therapy, he should have more frequent prothrombin times and the physician should be alerted. The patient should be instructed regarding this risk because he may take these drugs on his own or on the prescription of another physician who may not be aware of the details of his anticoagulant therapy. Phenobarbital has also been shown to have an effect on anticoagulant therapy.[24]

This consideration points up the importance of training each patient who is to go on anticoagulant therapy regarding various events that may be of new significance to him such as acute intestinal disturbances, alcoholic debauches, serious infections, and the use of drugs as mentioned above. If he is alerted to these factors, he may be more intelligent in his own approach to his regimen and in discussing it with other physicians whose services he may require.

Increased Understanding of the Clotting Mechanism

Today the most widely used prothrombin test still remains the Quick test with various modifications. This 1-stage test has been used as a guide in the treatment of many tens of thousands of patients and has served the purpose well. There are individuals who are more difficult to control or sensitive to anticoagulants. For them, more detailed studies of the various factors involved in the clotting mechanism are required. As a result of work in many laboratories a greater understanding

has been developed of the clotting mechanism and of the effect that anticoagulants of the coumarin and phenylindanedione type exert on certain factors beside prothrombin. The Quick 1-stage test not only measures factor II (prothrombin) but also factor VII (proconvertin) and factor X (Stuart-Prower) ac-globulin, and factor V to a lesser degree. Changes in factor VII, which generally precede those in the prothrombin activity, may be of the greatest importance in the therapeutic effect of anticoagulants of the coumarin or indanedione families. Factor IX may play some role in this anticoagulant action, and factor X also has a later effect. It is probable that other undiscovered factors also are active in this process. Changes in the less well recognized factors may result in unexpected episodes of bleeding or thrombosis when the patient is on apparently satisfactory anticoagulant therapy from the viewpoint of the prothrombin complex 1-stage test (Quick) alone. Therefore, other more sensitive tests have been developed. The Link-Shapiro modifications of the Quick test, especially with the use of a 12.5 per cent solution, results in a more sensitive determination of the effect of anticoagulants on the blood clotting mechanism. Owren has previously reported his work with the now widely used P and P test and has now developed a new method for the control of anticoagulant therapy, which is known as the "thrombotest."[25] The theory upon which this test is based is as follows:

The normal clotting of the blood occurs through partly separate systems called the "intrinsic and extrinsic coagulation systems." Clotting factors of the first system are all present in the circulating blood. These consist of factor II (prothrombin), platelets, the Hageman factor, factor VIII (antihemophilic factor A), factor IX (antihemophilic factor B), antihemophilic factor C, factor X (Stuart-Prower factor), factor IV (calcium), and factor V (proaccelerin). The coagulation is initiated by contact with foreign surfaces. It takes several minutes depending on the type of surface.

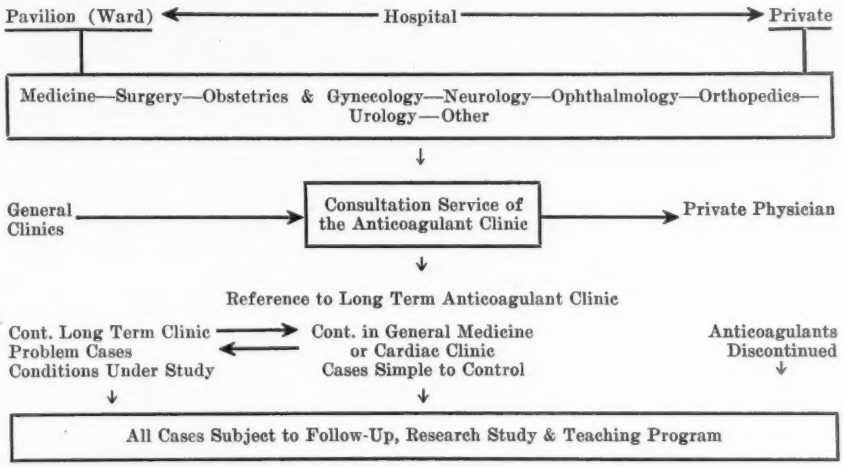
The extrinsic system is initiated by tissue fluid containing thromboplastin. This includes tissue factor III (thromboplastin), factor VII (proconvertin), factor X (Stuart-Prower factor), calcium, and factor V (proaccelerin). In the presence of an active tissue thromboplastin, blood clots in only 12 to 15 seconds and the activity of the slower intrinsic system cannot be detected under these conditions. During anticoagulant treatment with Dicumarol-like drugs, both the intrinsic and extrinsic coagulation systems are depressed; the former through reduction of factor IX (?), the latter through reduction of factor VII. Reduction of factor X and prothrombin influence both systems. Owren states that the new method includes a combined determination of all 4 factors that are depressed by the anticoagulant treatment. This new preparation consists of crude cephalin prepared by extraction of human brain or soybean, a thromboplastin prepared from animal organs, for example, ox or horse brain, absorbed bovine plasma that has been freed completely of the 4 factors, and calcium chloride in optimal concentration. All these ingredients are mixed into one reagent that is lyophilized and kept in vacuum in sealed ampoules. It is reconstituted with distilled water for testing in capillary blood and with weak calcium chloride solution for testing of citrated blood or plasma. The final reagent is opaque because cephalin and thromboplastin are insoluble in aqueous media and form a fine suspension. This material lyophilized and vacuum-sealed will keep for 12 months at room temperatures. The activity is unchanged after storage for 30 days at 47 C. After reconstitution the activity is constant for 12 hours at room temperature and for 3 days at 6 C. If the reagent is stored overnight in the ice box, it should be well mixed for further use. According to Owren, this material can be used for both capillary and venous blood and for citrated plasma. This technic constitutes a serious effort to provide the medical profession with a somewhat more comprehensive test that may prevent some of the hitherto unexplained complications of anticoagulant therapy. It is now under evaluation in many laboratories throughout the world.

Organization for Providing Long-Term Anticoagulant Therapy

It became clear some years ago that in order

Table 1

The New York Hospital-Cornell University Medical College Clinical and Research Anticoagulant Service


Pavilion (Ward)
Hospital
Private
Medicine—Surgery—Obstetrics & Gynecology—Neurology—Ophthalmology—Orthopedics—Urology—Other
General Clinics
Consultation Service of the Anticoagulant Clinic
Private Physician
Reference to Long Term Anticoagulant Clinic
Cont. Long Term Clinic Problem Cases Conditions Under Study
Cont. in General Medicine or Cardiac Clinic Cases Simple to Control
Anticoagulants Discontinued
All Cases Subject to Follow-Up, Research Study & Teaching Program

to provide adequate and comprehensive anticoagulant therapy in large hospitals, a team should be developed consisting of members who are thoroughly versed in the intricacies and the possible complications of anticoagulant therapy. Therefore, the Long-Term Anticoagulant Clinic of the New York Hospital was established in 1946. It was at first integrated with the Vascular Clinic, but soon outgrew this status and since 1950 has operated as a separate unit with overlapping interests and staffs. Dr. Ellen McDevitt has served as Chief of this clinic at the New York Hospital as well as a similar one at Bellevue Hospital since 1951.

The present organization structure (table 1) is as follows: Most of the patients on the hospital service who require anticoagulant treatment start this therapy while hospitalized for a thromboembolic state. They may be in the wards, semi-private, or private sections of the hospital. If any problem arises in the case of these cases, or if it is decided that long-term anticoagulation is desirable, the Anticoagulant Consultation Service is notified. With private patients this consultation is at the option of the patient's physician. Members of this service visit the patient, consult with the resident staff regarding a desirable regimen, and, if necessary, follow the patient, arranging for him to attend the anticoagulant clinic after leaving the hospital. A private patient may wish to continue with his own physician or if he and his doctor so elect, the control of his anticoagulant treatment may be assigned to a member of the anticoagulant staff in private practice. These patients may originally be seen on any service in the hospital. They may on occasion be started on anticoagulant treatment without previously being hospitalized if the indications seem clear. Patients who become part of the study group are assigned to the Long-Term Anticoagulant Clinic where they are seen at weekly intervals by a staff especially trained in this work. Some very stable patients are seen at intervals of 2 or even 3 weeks. If on anticoagulant therapy, their prothrombin tests are checked at these visits. As time goes on, each patient's regimen evolves into 1 of 3 patterns. If he requires continuous therapy and his anticoagulant control is not difficult, and if he is not a part of some special group under investigation at the time, he is transferred to the General Medical Clinic for continued care. This decreases the ever-growing

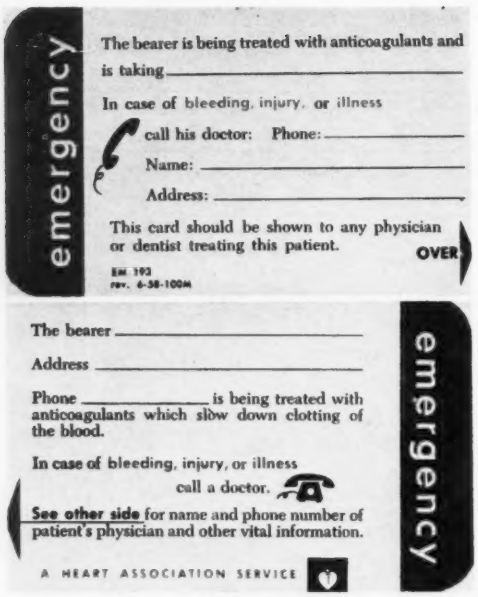

emergency
The bearer is being treated with anticoagulants and is taking
In case of bleeding, injury, or illness
call his doctor: Phone:
Name:
Address:
This card should be shown to any physician or dentist treating this patient.
OVER
EM. 193
rev. 6-58-100M
The bearer
Address
Phone is being treated with anticoagulants which slow down clotting of the blood.
In case of bleeding, injury, or illness
call a doctor.
See other side for name and phone number of patient's physician and other vital information.
A HEART ASSOCIATION SERVICE
emergency

Figure 1

Identification card for patients on anticoagulation therapy.

pressure on the Anticoagulant Clinic and it broadens the training of both students and other physicians in this technic. However, a member of the Anticoagulant Clinic is in constant attendance at the medical clinic to act as consultant and instructor and to handle any difficulties that may arise. If the patient proves difficult to control or has a condition that is under investigation, he remains assigned to the Anticoagulant Clinic under close supervision. If, as often is the case with thrombophlebitis, with a passage of a few weeks it is decided that anticoagulants should be discontinued, the dosage is gradually decreased and his anticoagulant care is terminated. He is then seen less frequently.

All patients are carefully catalogued. The natural history of these diseases is a major interest so that all patients are kept under surveillance and are included in the research and teaching program. This study also includes many patients treated for thromboembolic conditions by practicing physicians who are members of the staff. The Anticoagulant Clinic patients have their blood drawn on Tuesday mornings. About two thirds of them receive their dosage schedules for the next week or two before they leave the clinic. The others telephone Tuesday afternoons to receive their instructions. The same general routine is followed for private cases. It is important that each clinic and each physician undertaking anticoagulant therapy provide a 24-hour emergency service. Someone must always be on call. These patients are afflicted with diseases that frequently strike suddenly and brook no delay in medical care. Without anticoagulants, the stroke, myocardial infarction, or pulmonary embolus requires immediate attention regardless of the hour. While the use of anticoagulants reduces the risk of thromboembolic complications, it does introduce the need for a physician to be available at all times to advise regarding hemorrhagic manifestations. All patients carry a card of identification (fig. 1) obtained from the American Heart Association. It indicates that they are on anticoagulants and also gives the name, address, and telephone number of their physician or clinic. In addition, they are provided with a small supply of vitamin K_1, 5-mg. tablets. In the event of any major bleeding, they are instructed to take 2 of these tablets and call the doctor. This has been found to be a practical way of inaugurating early treatment, since hours may elapse before the doctor sees the patient.

It has been found most useful for the anticoagulant team to have conferences with the resident staff to review the technics used. An important conference is held during the first week of July when the new interns and residents first joint the staff. The meeting helps to develop uniformity of technic and a better liaison between the resident staff and the anticoagulant staff. The incidence of preventable complications has thus been markedly reduced.

Conclusions

1. The use of anticoagulant therapy in the treatment of acute myocardial infarction is generally accepted.

2. It should be used in most cases except

when contraindications or lack of facilities exists.

3. Heparin may be used in the initial stages of anticoagulant therapy, especially when there is need for rapid action.

4. The evidence now strongly favors long-term anticoagulant therapy after one or more myocardial infarctions in men. The evidence for its use in women is less conclusive but the available figures are too small for final evaluation.

5. The provision of adequate long-term anticoagulant care for those whose condition justifies its use is becoming a major social, economic, and technical problem. This is a challenge for the medical profession, the clinical pathology societies, the medical schools, and the public health services.

6. Evidence is accumulating that anticoagulant therapy favorably affects the incidence of morbidity and death in patients who suffer from angina pectoris due to coronary artery disease. Further studies are needed in this area.

7. It is possible to perform safely minor and even some major operations while patients are maintained on anticoagulant therapy. This reduces the risk of thromboembolic complications.

8. Patients on anticoagulant therapy should be given instruction regarding the effects of salicylates, antibiotics, other drugs, excessive alcohol, and various illnesses on the prothrombin activity.

9. The Quick 1-stage test carefully performed is satisfactory for most cases. However, many patients are sensitive, resistant, or otherwise difficult to control with anticoagulant therapy and for these more sensitive tests are indicated.

10. It is advantageous for hospitals to set up anticoagulant services in order to make available special knowledge regarding the problems that arise from this type of treatment and to help in obtaining maximum benefits from it.

11. An operating plan is presented as it functions at the New York Hospital. It is hoped that this will prove helpful to institutions considering the development of such a program.

Summario in Interlingua

1. Le uso de therapias anticoagulante in le tractamento de acute infarcimento myocardial es generalmente acceptate.

2. Therapias de ille genere debe esser usate in le majoritate del casos, excepte in le presentia de contraindicationes o quando le requirite equipamento non es disponibile.

3. Heparina pote esser usate durante le stadios initial del therapia anticoagulante, specialmente quando un action rapide es indispensabile.

4. Le datos usque nunc colligite argue fortemente in favor del uso prolongate de therapia anticoagulante post un o plure infarcimentos myocardial in masculos. Le situation es minus clar pro femininas; le casuistica non es satis extense pro permitter un evaluation definitive.

5. Le provision de adequate servicios de anticoagulantes a long vista pro le subjectos in qui su uso es justificate deveni gradualmente un major problema social, economic, e technic. Isto es un situation que demanda le attention del profession medical, del societates de pathologia clinic, del scholas medical, e del servicios de sanitate public.

6. Le indicationes se accumula que le therapia anticoagulante affice favorabilemente le incidentia de morbiditate e morte in patientes qui suffre de angina de pectore per morbo de arteria coronari. Studios additional es requirite in iste area.

7. Il es possibile interprender salvemente operationes minor e mesmo major durante que le patiente se trova sub therapia anticoagulante. Isto reduce le risco de complicationes thromboembolic.

8. Patientes sub therapia anticoagulante debe esser instruite con respecto al effectos de salicylatos, antibioticos, altere drogas, alcohol in excesso, e varie maladias super le activitate de prothrombina.

9. Le test uniphasic de Quick, si executate meticulosemente, es satisfactori in le majoritate del casos. Tamen, multe patientes es hypersensibile, resistente, o alteremente difficile a regular per medio de un therapia anticoagulante, e in tal casos methodos plus raffinate es indicate.

10. Il es avantageose pro le hospitales establir servicios anticoagulante pro dispensar informationes special con respecto al problemas que resulta ab iste typo de tractamento e pro assecurar le obtention de beneficios maximal ab illo.

11. Un plano de organisation es presentate como illo es in function al Hospital New York. Es sperate que isto va esser de valor pro institutiones que desira prender in consideration le elaboration de un tal programma.

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Thrombolytic (Fibrinolytic) Therapy for Coronary Heart Disease

By ANTHONY P. FLETCHER, M.D., AND SOL SHERRY, M.D.

THE COURSE of coronary artery disease frequently is altered by the development of acute thrombosis, a complication that plagues atherosclerotic vessels. Though progress has been made in treating this complication, current therapy is still far from satisfactory. Anticoagulants, effective though they may be in restricting further extension of the primary lesions or diminishing the incidence of new thrombi, have little influence on the obstructing thrombus or its direct consequences. For these reasons considerable interest attaches to any procedure that might produce a rapid resolution of the obstructing thrombus. A medical approach, currently receiving considerable attention, involves the use of thrombolytic or clot-dissolving agents and is aimed at enzymatic lysis of fibrin, the major insoluble fibrous protein of the clot. On the basis of experimental observations such an approach seems entirely feasible, and the present report briefly reviews the progress made toward the achievement of this goal. It will be apparent that therapeutic methods useful in coronary artery thrombosis are still in the early stages of development but concepts and methods of real promise are emerging. These latter aspects are stressed in this communication, since they are basic to further therapeutic advances.

Biochemical and Physiologic Considerations[1-3]

The disintegration of blood clot structure or clot lysis, which occurs when human blood clots are stored under sterile conditions, has long been termed fibrinolysis. Similarly, following sudden death, postmortem blood clots, formed through the vascular tree, dissolve over a period of several hours. Medical thought has been uniquely stimulated by such observations, for these spontaneous events of nature have implied that through proper use of physiologic enzyme systems, it might be possible to induce thrombolysis* in living subjects for therapeutic purposes.

Thrombi, as well as the serum, of all mammals contain a significant concentration of an enzyme precursor, plasminogen, which when acted upon by various specific activators, is converted to a proteolytic enzyme, plasmin.† Plasmin has a spectrum of enzymatic activity similar to but not identical with that of trypsin. Plasmin digests proteins of such physiologic importance as fibrin, fibrinogen, accelerator globulin, and some components of complement; alternative substrates, useful for assay purposes, include casein and certain synthetic amino acid esters.

Activation of plasminogen may occur spontaneously (under restricted laboratory conditions), but otherwise results from activation by specific kinases or activators. Such specific plasminogen activators can be extracted from all organ tissues, except the placenta and liver, and are found in plasma, urine (the urinary activator is named urokinase), and other body secretions. The ubiquitous presence of plasminogen activators in virtually all tissues and body fluids reflects the role of these substances in homeostasis.

The plasminogen-plasmin system seems admirably suited for effecting clot dissolution, not on the basis of any specificity of plasmin

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*The term thrombolysis will be used to describe the reaction by which thrombi (or clots) are lysed. The adjective thrombolytic will be used to designate biochemical moieties capable of inducing thrombolysis.

†Plasminogen and plasmin were for a brief period referred to as profibrinolysin and fibrinolysin. Happily this latter terminology, conveying an unjustified connotation of specificity, is now virtually obsolete.

for fibrin, but rather by virtue of the distribution of plasminogen and inhibitors. This distribution, dependent upon the separate location of plasminogen in either thrombi or plasma, profoundly influences the consequences of plasminogen activation.

Plasmin formed by activation of plasminogen within a thrombus has only fibrin available as its major substrate and is relatively uninhibited in its action. Thus activation of plasminogen to plasmin within the interstices of a thrombus results in extensive clot dissolution without any other manifestations of proteolysis. In contrast, plasmin formed in, or added to, plasma is usually rapidly inhibited by the large amounts of naturally occurring circulating antiplasmin. When unusually large amounts of plasmin are formed in plasma, then a number of plasma proteins may be acted upon without discrimination.

The Induction of a Thrombolytic State in Man

Physiologic Considerations

Theoretically there exist two approaches toward the therapeutic use of the plasminogen-plasmin system. Either the activated enzyme, plasmin,* could be infused into patients or alternatively, plasminogen activators could be similarly used.† In both instances, on theoretical grounds, increased activity of the plasminogen-plasmin system might be inferred to result; consequently either approach might, in theory, be a valid one. However, experiment reveals that the practical limitations inherent in the use of the enzyme plasmin are so great that the only feasible and indeed only physiologic way to incite increased plasma thrombolytic activity is to use plasminogen activators. The basis for this conclusion is examined below:

The Plasmin Approach[4, 5]

The top section of table 1 displays the simple theoretical concept that has been held to justify the use of plasmin infusion in patients. Though plasmin will digest fibrin under in vitro conditions, there are grave difficulties attendant on the use of this enzyme in vivo (bottom section of table 1). First, plasma exerts powerful inhibitory effects against plasmin; when extremely small doses of plasmin are injected (as in the clinical trials so far conducted with "plasmin preparations"), negligible enzymatic effects are produced in vivo. Second, and of much greater fundamental importance, is evidence that the infusion of sufficient doses of the enzyme plasmin to produce detectable enzymatic effects in vivo will cause a state of excessive plasma proteolysis or "fibrinolysis" as a disease state. Such conditions when recognized clinically (usually following operative procedures or obstetric complications) are associated with a hemorrhagic diathesis of severe and sometimes fatal intensity. The features characterizing this diathesis are shown in table 2, where it is indicated that they stem primarily from the biochemical lesion of fibrinogen proteolysis.[6] It is evident from in vitro experiment, from animal experiment, and from study of "fibrinolytic" phenomena occurring in human disease states[2] that the attempted therapeutic use of the enzyme plasmin is unlikely to prove effective in man. Similar considerations apply to the use of all other proteolytic enzymes so far tested. In all instances low doses of these substances are rendered biochemically inactive by plasma inhibitors; high doses, sufficient to overwhelm plasma in-

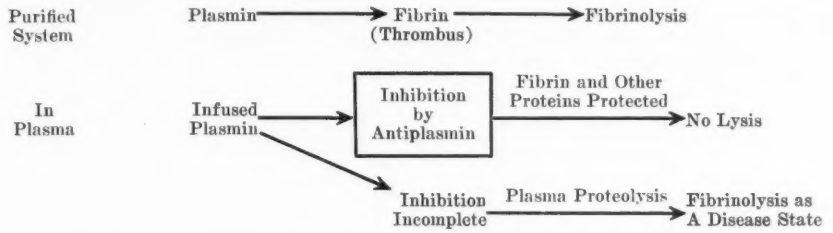
*This refers to the biochemical entity, plasmin, and not to the preparations under clinical trial or experimental study which also have been referred to as "plasmin." The latter are mixtures of activator (usually streptokinase) and human plasmin; the major portion of their fibrinolytic activity can be attributed to their content of activator.

†Another possible approach is to control the release of endogenous activator by pharmacologic agents. Though this may ultimately prove to be a useful method, the release of activator by pharmacologic means (nicotinic acid, bacterial pyrogens, etc.) so far has been inconsistent, variable in duration, and associated with the rapid development of tolerance.

Proteolytic enzymes (other than plasmin) currently available in purified form and capable of digesting fibrin also have been considered for thrombolytic therapy. Their use, in vivo, in amounts sufficient to produce clot dissolution probably will be extremely hazardous, if not catastrophic, for they have extensive effects on a great variety of plasma proteins.

Table 1

Dissimilar Effects of Plasmin in Vivo and in Vitro



The top portion of the table indicates that, in purified systems, plasmin degrades fibrin by enzymatic action. In plasma, because of the action of inhibitors, fibrin and other proteins are protected from enzymatic action (bottom portion of table). If plasmin is incompletely inhibited, proteins other than fibrin are degraded and "fibrinolysis" (excessive plasma proteolytic activity) occurs as a disease state.

Table 2

Coagulation Defect in Fibrinolytic Disorders

I. Effects of fibrinogen proteolysis	
Fibrinogen breakdown products interfere with fibrin polymerization.	A. Fibrinogen level reduced
	B. Thrombin time prolonged
	C. Prothrombin time prolonged
II. Decrease of factor V activity in plasma	

Pathogenesis of the hemorrhagic disorders in "fibrinolysis" as a disease state (effects of excessive plasma proteolysis). The decrease in factor V activity is of minor significance.

hibitory mechanisms, would induce a state of general plasma proteolysis and an associated severe coagulation defect.

The Plasminogen Activator Approach

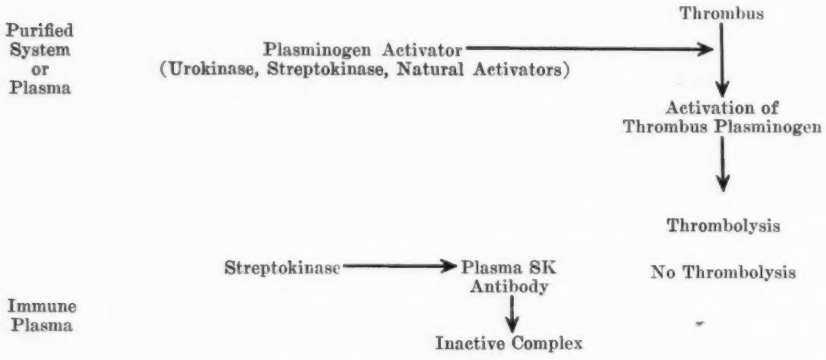
As indicated in table 3 (top section), plasminogen activators produce a thrombolytic action whether they are present in purified systems or in plasma. Substantial amounts of plasminogen are contained within the interstices of thrombi or fibrinous deposits and diffusion or absorption of a plasminogen activator to the thrombus causes activation of the intrinsic clot plasminogen and thrombolysis.[7] Though quantitative differences are apparent among the actions of the different activators listed in table 3, their qualitative modes of action are similar. The presence of plasminogen activator in plasma causes activation of plasma plasminogen as well as clot plasminogen, but clinical experience[8] has shown that plasma inhibitory mechanisms against plasmin are so effective that the resulting coagulation defect is usually of a minor nature.

The Induction of a Thrombolytic State in Man with Plasminogen Activators

To date streptokinase has been the only plasminogen activator prepared in sufficient quantity and purity for clinical trial. Its intravenous infusion has been shown to produce, both in man and animals, intensely heightened plasma thrombolytic activity, i.e., levels several hundred times the resting level.[8] There is indisputable evidence that the proper systemic use of this agent will produce lysis of experimentally induced thrombi in the experimental animal[9,10] and in man;[11] evidence of a less certain but highly suggestive nature indicates that streptokinase therapy

Table 3

Similar Effects of Plasminogen Activator in Vivo and in Vitro



The top portion of the table displays the mechanism by which plasminogen activators cause thrombolysis in purified systems or in plasma. However, in immune plasma, containing specific streptokinase antibody, the action of streptokinase may be inhibited (bottom portion of the table).

will lyse thrombi produced secondary to human disease states.[12]

Unfortunately, as is indicated in the lower portion of table 3, immunologic considerations arise when streptokinase is used for therapeutic purposes. Since streptokinase is antigenic to man and streptococcal infection is a relatively common event, human plasma contains a variable concentration of specific streptokinase antibody. Union of streptokinase and free antibody renders streptokinase biochemically inert and consequently, where therapeutic action is required, the initial streptokinase dosage, determined after titration of the patient's antibody, may vary over a wide range. The extent and importance of this fact has not always been realized by investigators who, as a consequence, have frequently used biochemically impotent preparations. When streptokinase is to be used as a therapeutic agent, it is mandatory to assay the patient's plasma for streptokinase antibody. In no other way can a dose be calculated that will produce a consistent biochemical response in man.

The literature, even that of recent date, abounds with claims that plasmin (sometimes called fibrinolysin) is an effective thrombolytic agent in vivo.[13] These claims are unsubstantiated and have arisen because of the use by several investigators of inadequately assayed and characterized "plasmin preparations." Adequate analytic methods reveal these preparations to be grossly contaminated with plasminogen activator (streptokinase) and the major portion of their in vitro biochemical activity can be attributed to the presence of streptokinase rather than plasmin. Consequently when such preparations are infused into man, their biochemical activity may be neutralized in the presence of specific antibody. Neglect of this fact has led to the marketing of a preparation described as human fibrinolysin (Actase) which, on infusion into man, exerts negligible biochemical effects.[14]

Solution of the problem of clot dissolution in man by enzymatic means requires, as its immediate objective, the institution and maintenance in vivo of a controlled biochemical state in which the circulating plasma of the patient is endowed with the ability to lyse preformed thrombi, yet without significant hazard or toxic effect. In this respect an analogy may be drawn to anticoagulant therapy in which the controlled state is one of hypocoagulability and the ultimate objective is

inhibition of clot formation. The purpose of this analogy is to stress the requirement for assay methods that measure the extent to which the thrombolytic activity of the patient's circulating plasma has been enhanced. Obviously such laboratory methods, in order to yield relevant data, should employ the patient's plasma and conditions that closely mimic the in vivo problem. Unfortunately much of the current work on fibrinolytic therapy is open to serious criticism, since observations of this type have either not been made or have been inadequately tested. In developing our own studies, we have relied heavily on a thrombolytic assay that measures the ability of the patient's plasma to dissolve preformed human plasma clots.[7]

Special Considerations in the Treatment of Coronary Heart Disease

The treatment of coronary artery disease and its complications by thrombolytic therapy present several difficult problems. First, it is evident that only the secondary complication of thrombosis rather than the primary arterial disease can be successfully treated in this manner. Second, it is known that coronary artery occlusion may be due to causes other than thrombosis and that diagnostic methods for making the distinction are lacking; arterial lesions such as those caused by subintimal hemorrhage could conceivably be worsened by the suggested therapy. Third, it is not yet firmly established that the restoration of blood supply to an acutely infarcted area of myocardium is always desirable. Finally, the therapeutic preparations used for the treatment of these often critically ill patients must be shown to be free of deleterious effect.

On the other hand, substantial benefits could follow the early enzymatic lysis of a coronary thrombus and the consequent restoration of blood flow to the acutely infarcted or acutely ischemic myocardium. These might include reduction of the final area of muscle infarction, reduction of the degree of electrical instability during the early critical stage of infarction, the prevention or removal of mural thrombi, and the prevention of extracardiac thromboembolic complications.

Animal Studies

Two groups of workers have studied the effect of lysing a thrombus obstructing a coronary artery by enzymatic means. Though in neither instance did the animal model approximate to the situation commonly found in the human, the results are of considerable interest.

Agress et al.[15] passed a catheter through the left carotid artery of dogs (closed chest preparations) and injected into the coronary arteries small fibrin particles, prepared from human plasma and sieved. Embolization with fibrin particles was continued until persistent and in some cases progressive electrocardiographic evidence of myocardial damage was observed. Half the dogs were treated with 1 to 6 intravenous infusions of trypsin over an 8-day period and the other half were maintained as controls. Comparison of treated and control animals suggested, by all the criteria used (degree of final infarction, presence of visible clots, degree of vessel patency, improvement in electrocardiographic findings), that the trypsin therapy had benefited the treated dogs.

Ruegsegger et al.[16] produced myocardial infarction in dogs by an open-chest procedure during which a serum-induced thrombus was formed in the anterior descending coronary artery. Systemic "plasmin" therapy, with a mixture of streptokinase and human plasmin, was administered within a few hours; after a variable time interval arteriographic evidence of partial or complete thrombus dissolution was obtained. The authors suggested that, as a result of the "plasmin" therapy, the final area of muscle infarction had been somewhat reduced in size and that judged on histologic grounds the degree of injury reaction was lessened.

The experimental results of these two groups, though failing to afford conclusive evidence of the benefits of enzyme therapy in experimental myocardial infarction, are of significance. Though details are lacking, it may be inferred from the data that hemostatic defects of a severe degree resulted from the state of general plasma proteolytic activity in-

duced by the enzyme therapy, yet in neither instance was excessive hemorrhagic reaction noted in the infarct. The implications of this finding may be relevant to the problem of enzyme treatment in the human.

Thrombolytic Therapy in Human Coronary Heart Disease

The clinical investigation of thrombolytic therapy in coronary heart disease, because of the many serious problems involved, has only recently commenced. Though the literature contains reports on the enzymatic treatment of only one small series of patients suffering from acute myocardial infarction, important information has already been obtained.

The purpose of the study[12, 17] was to evaluate the effect of a 30-hour period of intensive thrombolytic therapy in patients suffering from early myocardial infarction. Since there is theoretic reason to advocate the early use of enzyme therapy and some grounds for believing that its later use would be at least relatively ineffective, the patients were divided into a main early treatment group and a subsidiary late treatment group. The early treatment group comprised 19 patients whose infarct (judged on the basis of symptomatology) had occurred 5 to 16 hours previously (average 9 hours). The late treatment group comprised 3 seriously ill patients in whom infarction had taken place 34 to 65 hours previously and in whom enzyme treatment was only undertaken as a course of last resort; all died during or following treatment.

The early treatment group received intensive streptokinase therapy for 30 hours and were later maintained on anticoagulant treatment for at least the duration of their hospital stay. Serial biochemical measurements during the treatment period indicated that intensive plasma thrombolytic activity (100 to 500 μg. of fibrin lysed per hour per ml. of plasma) was developed and maintained for 30 hours. No patient died during the early acute phase, but 1 patient died from reinfarction 3 weeks later while receiving anticoagulant treatment. The mortality of the treated group was less than that of control patients selected by a double-blind procedure (4 of 11 died) and less than that of the hospital mortality during the same period (19.5 per cent). Nevertheless, because of the small numbers involved, statistical testing gave a p value of 0.2. Restudy of the group 4 to 6 months later revealed no evidence of aneurysm formation, and only minimal evidence of cardiac enlargement. Electrocardiographic findings were relatively favorable and neither the patients' symptoms nor physical examination disclosed unusual features.[12] Autopsy evidence revealed no finding suggesting that the treatment had exerted a deleterious effect on the myocardium.

Discussion

Hitherto the medical armamentarium has lacked measures to lyse thrombi or emboli within the vascular tree. Current investigation has progressed to the point where such measures may soon become available to the practicing physician. Since there are still a number of problems that must be solved before safe and effective agents can be made generally available, it has been the purpose of this communication to stress both present difficulties as well as encouraging results. The premature release of either impotent or potentially toxic agents will serve only to delay the ultimate achievement of practical thrombolytic therapy.

On the debit side, it is evident that enzymatic therapy is not sufficiently developed to permit its trial under any except clinical investigative circumstances. Clinical experience has been limited and methods are insufficiently standardized to permit an extended trial. Unusual difficulty has been experienced in preparing sufficient quantities of highly purified streptokinase (the only plasminogen activator so far tested) for large-scale clinical use. Current intense developmental work on this problem could prove successful in the near future, but at present each separate lot of streptokinase must be cautiously tested in man (to establish its freedom from pyrogenic impurity) before its serious therapeutic use can be contemplated. Streptokinase, because of its antigenic nature, is not an ideal plasminogen activator for clinical use; this prop-

city imposes certain restrictions upon and complicates its use, for individual patient dosage must be established after prior assay for plasma antibody.

On the credit side it can be claimed that recent contributions to physiologic knowledge have not only elucidated the mechanism by which clot lysis proceeds in vivo, but have emphasized the considerable possibilities inherent in the therapeutic employment of this mechanism. The control in patients of thrombolytic mechanisms has proved to be possible, though at present the laboratory tests required for this purpose are still of an undesirably complex nature. The limited clinical evidence not only supports the feasibility of this therapeutic approach but, perhaps more important for coronary heart disease, it indicates that enzymatic treatment is not associated with deleterious secondary effects on infarcted myocardial tissue. Consequently, in principle at least, large-scale trial of enzymatic therapy in coronary heart disease may be indicated, though this should await the solution of certain technical problems. Undoubtedly the greatest need for the future is for the development of a nonantigenic plasminogen activator; current work with urokinase (the naturally occurring urinary plasminogen activator) offers promise in this connection.

It is the authors' conviction[18] that the establishment of sound scientific principle should take precedence over practical trial based on poorly controlled or empirical observations. Recent progress with the former aspect has been gratifying and therapeutic principles now seem to be firmly established; it may be anticipated that their practical application will follow shortly.

Summario in Interlingua

Usque nunc le armamentario medical ha includite nulle mesuras pro effectuar le lyse de thrombos o embolos intra le arbore vascular. Le investigationes currentemente in progresso ha attingite un puncto ubi nos pote predicer que tal mesuras va tosto esser disponibile al medico practic. Proque il remane un numero de problemas que debe esser resolvite ante que salve e efficace agentes pote esser lanceate al uso general, le objectivo del presente communication esseva signalar tanto le difficultates ancore existente como etiam le incoragiante resultatos jam obtenite.

Al latere negative, il es evidente que le therapia enzymatic es non ancora sufficientemente disveloppate pro justificar su application excepte intra le quadro de un investigation clinic.

Al latere positive, on pote insister que recente contributiones a nostre cognoscentias physiologic ha non solmente elucidate le mechanismo que representa le lyse del coagulo in vivo sed ha etiam fortificate nostre fide in le possibilitate de traducer ille mechanismo in un forma de exploitabilitate therapeutic. Le regulation del mechanismo thrombolytic intra le patiente se ha provate effectuabile, ben que al tempore presente le tests de laboratorio que es requirite pro ille objectivo es ancora de natura regrettabilemente complexe.

Il es le conviction del autor que le establimento de solide principios scientific debe preceder le essayos practic a base de observationes mal regulate o purmente empiric. Recente progressos con respecto al principios es promittente. Le theoria therapeutic pare esser firmemente establite, e le expectation es justificate que su exploitation practic va tosto sequer.

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Legal Aspects of Coronary Disease*

By HOWARD B. SPRAGUE, M.D.

Felix, qui potuit rerum cognoscere causas. (Happy the man who has been able to understand the cause of things). Vergil, Georgics, Bk. ii. 1.490.

THE PATIENT with coronary disease comes into court, or his descendents for him, mainly under 3 major conditions: (1) it is claimed that he has received a personal injury which caused or aggravated his heart disease; (2) his cardiac mischief has been produced or worsened by his employment (Workmen's Compensation); or (3) he is entitled to premature pension payments, governmental or private, by virtue of an occupational hazard to his heart.

In a case carried to the Supreme Court of Minnesota which was, however, not a cardiac problem, the Court said "Since we as judges lay no claim to expertness in these matters [the etiology of cancer], we can add nothing to the discussion, nor can we be expected to resolve these conflicts which the medical profession itself has been unable to resolve. Notwithstanding this uncertainty, we think we are bound to treat the opinions of these doctors as something more than speculation and conjecture, which are but polite terms for unscientific guesswork."[1]

And as Larson says "Plainly, the heart cases will continue to be troublesome as long as some reach the appellate courts on a record in which the medical testimony is emphatically certain that effort and exertion have nothing whatever to do with coronary thrombosis, while most such cases are based on the opposite thought."[2]

Thus, the reason for litigation, in the cases of coronary disease, is referred to differences in opinion within the medical profession. The skepticism of lawyers about medical disagreements is illustrated by Lambert's belief that it is best to have adversaries in court rather than panels and "impartial" physicians, in these cases, since "the expert ism of today becomes the wasm of tomorrow." So litigation will go on, for, according to Justice Holmes "our ideal may be repose, but our destiny is effort."[3] It should be remembered that Holmes lived to the age of 94.

There are influences, foreign to medical thinking, which color the legal aspects of the coronary problem, but which, none the less, physicians should understand. The first of these is the difference between the lawyer's and the doctor's definition of causation. This has been well discussed by Small.[4] The physician, indeed, must undergo an almost mystical revelation to accommodate his thinking to that of the legal profession as it relates to causation. "But," as Small says, "the lawyer and the doctor have so pontificated over simple words, so preened them and institutionalized them, that the layman thus put in the dark, is as wise as the lawyer and the doctor when each is confronted with the other's busywork." "The lawyer simply is not after the same cause as the doctor, and therefore cannot be expected to reach the same causal ends." This is perhaps even more striking in the case of Workmen's Compensation than in personal injury actions, because of what Horovitz rightly calls "the litigious phrase: 'arising out of' employment."[5]

The lawyer complains that the doctor has "difficulty in separating cause from etiology" whereas "lawyer—cause, whatever modifier be used, can have no meaning except that which it takes from the system, the system represented by the concept-term, Law. As that system is one of adjustment toward social harmony, certain policy considerations will inescapably control the adjustment process—policy considerations springing from social demands."[4]

*The Peter T. Bohan Lecture, delivered at the Alumni Day meeting of the University of Kansas Medical Alumni Association, Kansas City, Kansas, June 4, 1960.

Thus, "the defendant's part in the misfortune need not have been its sole cause, or even its principal cause, but only a cause of sufficient proportion, in the light of his conduct, to make it seem just for him to shoulder the cost."

It is in this phrase "policy considerations springing from social demands" that one sees the other chief influence affecting litigation of coronary heart disease. The physician attempts to have a scientific attitude toward causation, the lawyer's motivation is the socially desirable one of relieving the burdens of physical harm and economic tragedy. It is true that the physician at times descries in this yearning solicitude of the lawyer for humanity a certain element of crocodilian lacrimation when juries are notably generous on a contingent fee basis with attorneys' fees taking up to one third of the award; but how else could the indigent receive such skillful legal advice, is the lawyer's reply.

The tort, or personal injury cases, are of many sorts, from the fatal coronary thrombosis secondary to a shocking accident, to the exacerbation of angina from the mental stress of witnessing an altercation.

But it is not so difficult for the physician to attempt an assessment of the factors in such cases as it is for him to try to appreciate the change that has occurred in the purpose of Workmen's Compensation Laws.

Even among lawyers there seems to be a difference of opinion about the genesis of these statutes—one side believing them to be the outgrowth of older common laws concerning personal injury, but the most vocal advocates asserting that Workmen's Compensation has nothing to do with "tort law," "scope of employment," "proximate causation," "foreseeability," "assumption of risk," or "blameworthiness"—all factors in personal injury actions. As Riesenfeld says, it "is fundamentally a branch of social insurance, designed to protect a segment of the population against sub-standard living conditions brought about by a typical hazard of modern society."[6]

Perhaps the most active defender of this concept of Workmen's Compensation is the National Association of Compensation Claims Attorneys, often called NACCA. Its journal is a rich source of material for tracing the historical development of the interpretation of the law as it relates to financial recompense for personal injury, and other forms of compensation. Similarly, Arthur Larson's "The Law of Workmen's Compensation"[2] is the constantly current loose-leaf reference work of the highest authority.

Workmen's Compensation legislation started in Germany in 1884 as a part of state socialism to compensate the injured worker. Britain followed in 1897, Maryland had a Cooperative Accident Fund in 1902, Massachusetts set up its first commission to investigate the subject in 1904, the Federal Act was passed in 1908, in 1911 ten states passed Workmen's Compensation laws; finally in 1948 the last State, Mississippi, had joined the system.

The development of Workmen's Compensation differs in various countries. The British law originally defined the purpose in much the same way as do most of our present State statutes, namely, recompense for personal injury "by accident arising out of and in the course of employment." But it has become an "enterprise liability." "The enterprise of employment is responsible for harms occasioned by it." It is an entirely new social principle of "liability without fault." Or as Lloyd George is credited with expressing it, "The cost of the product should bear the blood of the workingman."[6]

Larson,[2, 7] as United States Undersecretary of Labor, states the underlying philosophy as it applies in this country, at least in the vision of the welfare state, "Workmen's Compensation is one segment or department of the overall pattern of income-insurance, which includes unemployment insurance, sickness and disability insurance, and old age and survivors insurance." This concept is obvious in England, Australia, and New Zealand. The American system is unique in that it "is neither a branch of tort law nor social insurance of the British or Continental type," but

as some of the characteristics of each. It is 'social in philosophy'' but ''largely private n structure.''

It will be seen that nonoccupational dis- bility is the only interruption of employment ot yet generally covered by insurance in this ountry, and in this fact lies the growing odification of Workmen's Compensation ulings toward making it a type of over-all overage for disability of any sort, and hrough this painful, Procrustean process hronic degenerative diseases, such as coron- ry artery disease, enter the field. The de- fense of the admission of these diseases as industrial accidents is that the people demand it; but this erosion of the concept of ''indus- trial accident'' has placed the medical pro- fession in an untenable position.

How has this come about? By the process through which all law develops. As Roscoe Pound said, ''The law grows by judicial ap- plication of reason to experience,'' and he points out that ''the legislation of the social service state is, one might put it, changing the center of gravity of the law.''[8]

Several very provocative decisions have almost succeeded in dominating legal prece- dent in cardiac, and especially coronary, cases. I say ''almost,'' because decisions of appel- late courts differ not only between states, but within the same state, or even within the same court. But certain features have become firmly established.

In the first place, in 1903, an interpretation was rendered by the British House of Lords of the term ''by accident'' to include the *re- sult* as well as the *cause*.[2] Therefore ''the 'by accident' requirement is now deemed satis- fied in most jurisdictions either if the cause was of an accidental character or if the effect was the unexpected result of routine perform- nce of the claimant's duties.''

Also it is a legal principle that the employer takes the employee as he finds him.'' That to say, there is no provision for the ''idio- ncratic individual'' who may well be the ubject of chronic disease at the time of em- loyment, an argument of some weight in favor of pre-employment medical examina- tions.

There are 4 categories of employers liabil- ity for accident (Larson):[2]

1. The liability *usually* holds when some- thing ''lets go,'' such as hernia, cerebral hemorrhage, arterial or blood vessel rupture, ruptured aneurysm, apoplexy, etc.

2. In injury from generalized conditions during routine exertion the courts are less definite. These include coronary thrombosis, myocarditis, dilatation of the heart, and arte- riosclerosis.

3. Routine exposure resulting in freezing or sunstroke is usually admitted.

4. The weakest category, so far as proof of accident is concerned, is routine exposure causing disease, such as pneumonia, rheuma- tism, nephritis, etc.

In the cardiac field a major legal tussle has taken place over the point as to whether or not an unusual degree of stress has occurred to precipitate the attack, usually angina, coronary occlusion, or acute congestive fail- ure.

Georgia has carried its legal conclusions to the ultimate stage and its court has said ''an accident arises out of employment when the required exertion producing the accident is too great for the man undertaking the work, whatever the degree of exertion or condition of health.'' In this State, heart failure has actually been held to be an accident even when the exertion was lighter than usual, as long as it was considered to have precipitated the attack.

This principle is accepted in New York, especially since the Masse case (1950), when it was held that ''whether or not a particular event is an industrial accident'' is to be de- termined, not by any legal definition but by ''the common sense viewpoint of the average man.''

That legal jurisdictions in the United States are not consistent in awarding compensation for disability from ''general conditions,'' in- cluding heart disease, is seen by the fact that 19 award such compensation and 13 deny it.[2] It is admitted that there is a fear on the part

of Workmen's Compensation Boards and the Courts that the heart cases will get out of control and that this sets some arbitrary boundaries for their decisions. They really do not want to compensate for deaths not actually caused in any substantial degree by employment. In general, there must be an unexpected result, and there must be some exertion capable, medically, of causing collapse. Yet how liable to disputation is the classical pronouncement of Chief Justice Rugg of Massachusetts in 1914: "Acceleration of previously existing heart disease to a mortal end sooner than otherwise it would have come is an injury within the meaning of the Workmen's Compensation Act."[14, 15]

The physician views some of these decisions with amazement. In one case a man fractured a heel bone in a fall and was said to have had pain and to have been anxious. He died 3 months later of a coronary thrombosis. Only 1 of 5 doctors who testified thought there was any connection, but the Board chose this one's opinion and held for the plaintiff.

In another instance, a judgment was given for the plaintiff on the basis that a coronary thrombosis, allegedly due to lifting, lowered his "resistance" so that he died of cancer of the bladder.

Courts have found for the plaintiff when he suffered a heart attack during an altercation in which he was the aggressor. This element of contributory negligence has disappeared from Workmen's Compensation, an extreme example being the recovery of financial recompense by the heirs of a laundry man who was shot and killed by a testy husband who objected to the plaintiff regularly collecting his wife's amorous favors, as well as the laundry. It was held that he was on the job at the time and therefore entitled to Workmen's Compensation for an occupational hazard.[17]

Medical testimony may be completely ignored by the Court, and it is true that appeal boards tend to uphold compensation boards even in the absence of "a single shred" of medical evidence of causal relation.[16]

A truck driver may work long hours without regular sleep and gain 40 pounds in weight, yet if he has a heart attack the decision may imply that his work alone was the cause of his death. "Presumption as to cause," says a Tennessee Court, "should be resolved in favor of the employee."

As Workmen's Compensation expands it has entered an umbrageous area concerned with injury from emotional stress. In Massachusetts, this principle was held valid for the death of a motor vehicle inspector from a coronary attack occurring 1 or 2 hours after a supposedly stressful interview with the survivor of an accident. No testimony was submitted that the interview was emotionally disturbing. The Supreme Court merely decided it must have been![15]

No one would deny the influence of an acute emotional stress in precipitating an attack of angina, but the assumption of stress as the cause of atherosclerosis or hypertension is scientifically unwarranted and socially dangerous in its implications. Furthermore, coronary thrombosis to be attributed to an emotional episode must, it seems to me, show its onset by symptoms appearing at the time of the stimulus or in relation to some measurable alteration in heart rate, blood pressure, or other significant vital index, which continues unabated after the episode. No one has shown convincingly that local alterations in the coronary vessels (such as subintimal hemorrhage or rupture of atheromatous abscess), or hypercoagulability of the blood in these vessels, are related to either physical or mental stress.

In the United States Public Health Service Study in Framingham, for example, about one third of the new attacks of clinical coronary disease were revealed by sudden, unexpected death in the course of the accustomed lives of the victims, and about 20 per cent of new coronary events were revealed by electrocardiographic evidence in the absence of any convincing history of cardiac pain.

There is one other compensation area into which coronary disease has entered by frontal attack. This is the disability pension system through the passage of so-called "heart laws,"

applying to certain categories of State employees. The Massachusetts Act may serve as an example. It has removed opinion concerning causation from the medical field and placed it in the legislature, because this law states that if certain State employees develop heart disease or hypertension, it is to be presumed that these conditions are service connected, that is, arising from the character of their employment, and such select individuals are to be retired at any time with the special pension privileges enjoyed by other employees retired for accidental disabilities. The favored groups at present include firemen; policemen; employees of the Registry of Motor Vehicles who perform police duty; employees in the Department of Correction whose duties require supervision of prisoners, criminally insane or defective delinquents; crash crewmen; crash boatmen; fire controlmen or assistant fire controlmen at the Logan Airport.

Such presumptive legislation is another example of the erosion of the role of the physician in determining the relationship of an occupation to disease. It matters not that there is no significant evidence that these specific occupations are associated with premature or enhanced incidence of hypertension or coronary disease; it is only important that the voting of these groups be powerful. The members of the Legislature wish also that their stressful devotion to lawmaking be recognized by inclusion of themselves under this law.

To some degree the medical profession is responsible for its sorry state. It has permitted medical testimony to be submitted in court which has been so far from reasonable that it has cast doubt upon all medical testimony. As a result, affirmations of no scientific value are accepted on the same basis as those of high authority. As Hubert Smith phrased it, "Courts have plodded along, quite willing to recognize any holder of an M.D. degree as a universal expert on science. This naïveté is surprising, for the same judge who rules a general practitioner competent on his qualifying or voir dire examination, will take the train for Mayo Clinic if he stands in need of specialized surgery!"[9] Courts and legislatures conclude that social pressures are such that they might as well decide causation by judicial or legislative fiat as to weigh conflicting medical opinion. Only occasionally does a court assert that mere possibility of causal relationship is not enough to sustain a finding.

In the Supreme Court of the State of Washington, for example, a judgment was ordered for the plaintiff's heirs because he was found dead 40 minutes after the end of his working day, during which he pulled levers. A physician had testified that "the fatal attack was precipitated by some physical activity which caused the clot, shown to be of long standing, to let loose."[18] The right coronary artery was shown at autopsy to be occluded by a thrombus. Is there any wonder that such evidence makes high court pronouncements about causation meaningless, as one from the Supreme Court of Idaho, "evidence of likelihood is enough"; especially, as Smith says, since "some medical witnesses are venturing opinions in Court which they would not assert before medical societies."

Lay bugaboos become enshrined and used as precedent, as in a Tennessee case, "The Court takes judicial notice that climbing of stairs is condemned by the medical profession as among the activities most harmful and dangerous to persons afflicted with heart trouble and arteriosclerosis." This is similar to the superstition about the danger to cardiac patients of raising the arms over the head.

Is this uneasy medicolegal situation likely to continue? Can any principles be promulgated concerning the relationship between overt coronary disease and the environmental influences subject to litigation?

It seems to me that the American system favors adversary action in the courts for an indefinite time. Certainly this is true in personal injury cases, since they must remain so highly individualized.

The American Heart Association has a Committee on Strain and Trauma which, for several years, has been investigating the medical and the legal aspects of the whole prob-

lem. As a member, I know the difficulties it faces, and the uncertainties of defining scientific proof. The precipitation of an attack of angina, fatal or not, can reasonably be shown at the time of an unusual event, but the relationship of such an event to the clinical pattern of coronary occlusion and myocardial infarction is much more obscure.

Blumgart[10] has stated the situation clearly: "Recognition of the causal relationship of effort to acute myocardial infarction should not lead the medical officer or physician to ascribe every attack of acute myocardial infarct to preceding effort. The occurrence of acute myocardial infarction in the foregoing cases during or immediately after strenuous effort clearly establishes a causal relationship. As with most diagnostic problems in medicine, the relation of effort to an attack of acute myocardial infarction in a particular patient may be certain, may be probable, suggestive or improbable or may be considered to be nonexistent.

"The relation is considered definite if the following criteria are satisfied:

1. The development and increase of cardiac symptoms such as pain or substernal distress during or immediately following unusual effort.
2. Continuation of symptoms after cessation of effort.
3. The presence of the clinical signs and symptoms of acute myocardial infarction.
4. Development of the characteristic electrocardiographic pattern of acute anterior, posterior or lateral wall infarction."

Regan and Moritz[11] have also delimited the influence of trauma and stress on heart disease. In the Editorial Comment accompanying a reprint of this article in the book of Moritz and Helberg, the opinion is given that "If a medical witness is to be justified in attributing the disability for which compensation is claimed to some specific episode of trauma, he should have valid reasons for believing that the same degree or kind of disability would not have developed at the time that it did were it not for the specified traumatic event. This means that the witness should be able to defend the proposition that the particular manifestation of the disease for which compensation is claimed was not consistent with spontaneous occurrence and was, therefore, caused or contributed to by the effects of the trauma."

The much bolder concept that occupations as such, especially the so-called emotionally stressful ones, are responsible for coronary artery atherosclerosis and disease is entirely lacking in proof. Regan and Moritz state "In no circumstances can stress or injury be held accountable for coronary-atherosclerosis." A great cult of stress is being developed in this country, aided by reports that, under conditions of emotional pressure, serum cholesterol rises and coronary troubles ensue. Gofman[12] has recently shown, however, that in one of these studies the rise in serum cholesterol was completely explicable on the basis of the admitted fact that the victims (accountants) under stress ate more.

Whether or not we are ready to admit overeating and physical inactivity to the category of industrial hazards is questionable, yet this would seem to be true, for political purposes, in the passage of "heart laws." However, there would appear, in fact, to be more evidence that the energetic stressful reactive life has protective value, but since it is impossible to titrate emotional stress the conclusions of "stress" studies are largely meaningless.

In the field of Workmen's Compensation one cannot disregard the pressure to include the degenerative diseases in compensable injuries, simply on the basis of social desires. Dawson has called this "a distinctively North American development." It is of interest, however, that there is a tendency for some of the labor unions at times to deny occupational relationship because the benefits under sickness disability insurance provided by some companies are greater than under Workmen's Compensation. Similarly, we have seen one pressure group, successful in obtaining special favors under the "heart law" of Massachu-

setts, now objecting to the extension of the law, to include further categories of State employees, for fear that the pension funds will be unable to bear the rapidly mounting expense.

It is to be hoped that some solution will be reached, since not only is the potential liability for coronary disease enormous in the American pattern of life, but the need for rehabilitation and employment of cardiac subjects and older workers demands a classification one way or another, either coronary disease is to be considered occupational and included in Workmen's Compensation or it should be provided for by some form of sickness disability insurance. One may present as many difficulties as the other, since sickness insurance is notoriously subject to abuse, but this sickness cash-benefit insurance exists (1951) in 5 states and under the Railroad Unemployment Insurance Act.

One senses a certain apprehension on the part of some lawyers that litigation may diminish if compensation cases are too readily adjudicated, but a further source of litigation has been suggested, namely, that even when Workmen's Compensation payments are granted to the employee he should also be allowed to return to his old common-law privilege of suing the employer in addition, if the latter has been negligent. I have seen no such solicitude for the employer when the worker is negligent.

The position of the physician in this whole picture is truly anomalous. He is still necessary for the process of the law but his testimony is accepted or rejected often quite cavalierly by the courts, and in relation to the social philosophy of the geographic area.

Of course the doctor who has treated the plaintiff is in a difficult situation and may be subject to the dichotomy of loyalty to his patient vis-à-vis his scientific conscience. There may be the desire to be a "good fellow," or even the knowledge that a favorable judgment would ensure his medical fee, or an unfavorable result, for want of his support, might lose him his patient.

On a less subjective level the medical man is forced to realize that in many cases he cannot be dogmatic about causation or aggravation. He can only offer his considered judgment and there is no question that a well-trained practitioner may know his patient better than the specialist. However, this does not excuse the practitioner or the expert from giving evidence so far from accepted scientific knowledge as to discredit the profession. It has even been suggested that a special committee of the state medical society review the recorded testimony of all physicians in court to determine their honesty or venality.

The Moreland Commission of New York[13] in 1957 studied the cardiac problem and from the answers of 398 internists and cardiovascular specialists they concluded, in part, that "work does not produce heart disease (93.9% against 1.5%); performance of the same type of moderately heavy work without engaging in unusual exertion or strain has no injurious effect upon the heart. A myocardial infarction occurring during such work is not causally related to the employment (88.6% against 7.1%)."

This is at least highly competent medical opinion, but the difference in probative weight between medical judgment and judicial decision is illuminated by a Kansas case where it was held that compensation should be granted to the plaintiff since, "if his physical structure gives way under the stress of his usual labor, his death is an accident."

To the physician it appears more reasonable to allot a certain percentage of disability to an occupational aggravation of a chronic disease. This is the practice in California, Kentucky, and North Dakota. Above all, insistence upon an autopsy in death cases is, I believe, imperative.

Finally, the doctor is at a disadvantage in that he must maintain a scientific attitude—his greatest strength lies in this—but in Smith's phrase "the anvil of the law has always resounded to the striking iron of science" and "few members of the populace can have failed to hear the reverberating blows or to see the cascading sparks which fly from these impacts." He thinks that the

lawyer, the doctor, and the man of science "may find themselves companion toilers on a more intricate pattern called 'social synthesis.' "[9]

What I wish to emphasize by this quotation is that the physician should have as much right as the lawyer to think in terms of this "social synthesis" within the rigorous confinement of scientific observation. The lawyer may rationalize his endeavors to prove that his client's occupation disabled him with a coronary thrombosis, and therefore that he should be paid, as contributing to the higher good, but the physician should also allow his broader viewpoint to prevail in denying the relationship, in the absence of reasonable evidence, with the hope that the social pattern would thereby be improved by lowering the barriers of the economic fear of employing cardiac subjects.

It does no good for the doctor to consider the lawyer ridiculous or nefarious, nor for the lawyer to think of the doctor in court as unsure, indefinite, or merely an instrument on which to play his tune.

When all is said and done, public opinion and social demands will determine the interpretations of the courts. The medical and legal professions stand as great symbols of free and individual enterprise. Both bid fair to lose status in a socialist polity but the physician especially is speeding the coming of this state if he fosters the establishment of a legal precedent that work is always an evil and must perforce accelerate chronic disease. He should instead stick to his scientific guns and let the evils of poverty, chronic nonoccupational disease, and misfortune be alleviated by other processes than by forcing him to accommodate his medical knowledge to the purposes of the social-service millennium.

Summario in Interlingua

Exemplos ab le sphera del morbos cardiac es usate pro illustrar le argumento general que le concepto medical de causa como factor etiologic e le concepto legal de causa como factor responsabile non es identic. Le autor deplora le progressive degeneration del testimonio medical in casos de compensation pro accidentes occupational. Ille analysa le situation in omne su ramificationes super le base del conviction que le rolo legal del profession medical non pote restablir su dignitate si le medicos mesme non apprecia le fortias e tendentias extra-medical—i.e. social, sociologic, e mesmo socialista—que codetermina le functiones del cortes.

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CLINICAL PROGRESS

Atrial Repolarization—Its Importance in Clinical Electrocardiography

By JOAO TRANCHESI, M.D., VICTOR ADELARDI, M.D., AND JORGE MARTINS DE OLIVEIRA, M.D.

SINCE the studies of Abramson et al.,[1] the atrial repolarization has attracted the attention of several investigators.[2-6] In spite of this, we believe that not enough emphasis has been given to its significance in the everyday electrocardiographic diagnosis.

The importance of considering the electrical activity of the atria for the correction of the isoelectric line in the determination of the QRS and T areas has been pointed out.[7] Similarly, the role of the atrial repolarization in the displacements of the S-T segments has also been discussed.[4]

In the present paper we have considered the atrial repolarization as a whole, calling particular attention to the changes observed in the atriogram itself as well as to those produced in the ventriculogram.

Atrial Repolarization

In cases of atrioventricular block, it is possible to observe that immediately after the P wave, there is another wave, flat and of slow inscription, which is conventionally called the atrial T or Ta (fig. 1). The Ta wave has a direction opposite to the preceding P. This indicates that the vector of atrial repolarization must have an upward, rightward, and slightly backward orientation (exactly opposite to the vector of atrial activation). Since the areas of P and Ta are equal, but of opposite polarity, the resultant vectorial summation—atrial gradient—is equal to zero.[3] This differentiates physiologically the atrial from the ventricular electrical phenomenon. Another difference exists in that, in the atria, the propagation of the waves of excitation and recovery are parallel to the muscular walls, and not perpendicular as in the ventricles (fig. 2). This can be explained by the fact that the thinness of the atrial wall allows equilibrium in pressure and temperature between the epicardial and endocardial surfaces of the atria.[3, 8] Consequently, the processes of atrial activation and repolarization start from the same region, the sinus node, and therefore no gradient is expected.

The segment that is inscribed from the end

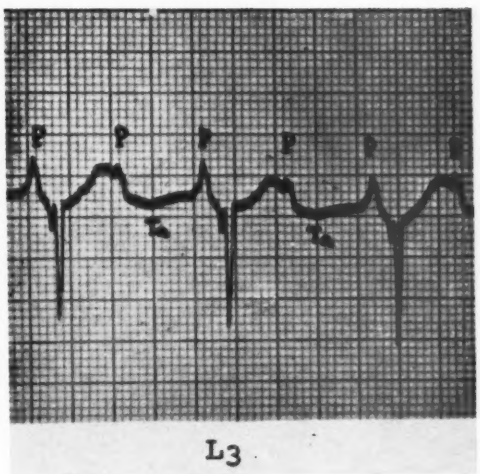

Figure 1

Second degree atrioventricular block. The Ta wave is easily identified. The P-Ta interval is equal to 0.24 second. The ventricular J point is displaced downward.

From the Electrocardiographic Department, Hospital das Clinicas, S. Paulo, Brazil, and St. Vincent Charity Hospital, Cleveland, Ohio.

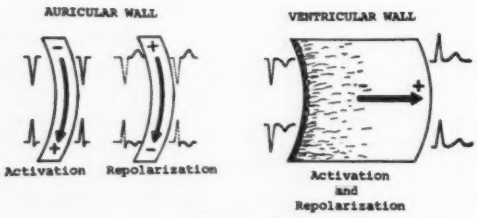

Figure 2

The atrial activation and repolarization processes are parallel to the atrial wall, while the ventricular activation and repolarization processes are perpendicular to the ventricular wall. The atrial electrical phenomena display similar morphology in both endocardial and epicardial atrial leads.

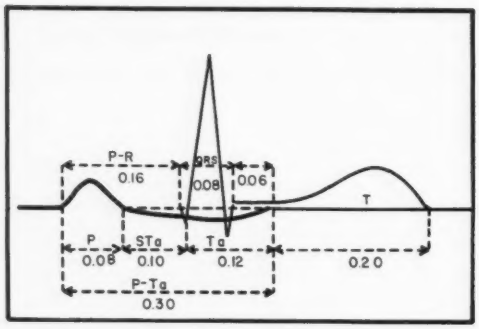

Figure 3

The time relationship between the atrial and ventricular electrical processes.

of the P to the beginning of the Ta wave is called the S-Ta segment. This segment is recorded during the P-R interval and the beginning of the QRS complex, while the Ta wave is superimposed on the final part of the QRS and on the S-T segment (fig. 3).

It must be pointed out that the P-R segment, apparently isoelectric, may actually show, even in normal cases, a slightly downward displacement (mainly in lead II).[8-10] The magnitude of such a displacement may reach 0.08 mv., and is proportional to the area of the P wave and to the cardiac rate.[11] The atrial electrical systole, which is the summation of all atrial electrical phenomena, is called P-Ta and corresponds to the ventricular Q-T interval. Its normal values have been described as ranging between 0.15 and 0.45 second.[8]

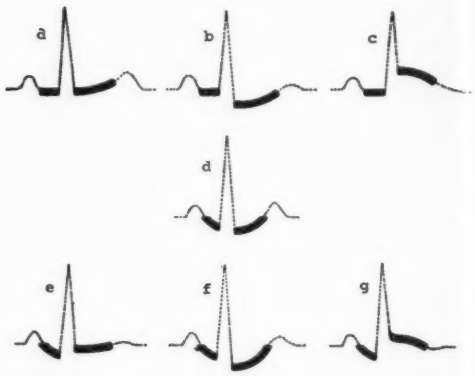

Figure 4

Relationships between the displacements of the P-R and S-T segments. (a) *Normal.* (b) *Subendocardial ventricular lesion.* (c) *Subepicardial ventricular lesion.* (d) *Sympathetic effect.* (e) *Atrial lesion or sympathetic effect plus mild subepicardial ventricular lesion.* (f) *Sympathetic effect plus subendocardial ventricular lesion.* (g) *Sympathetic effect plus marked subepicardial ventricular lesion.*

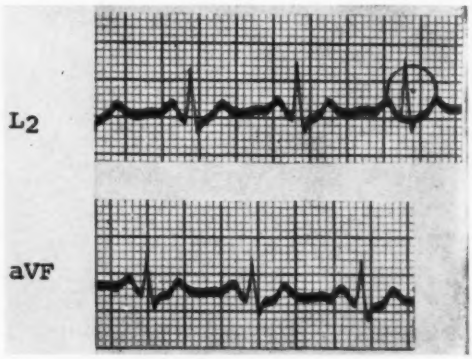

Figure 5

Exercise tolerance test in a normal individual. The downward displacement of the S-T segments is not due to any pathologic condition of the ventricular myocardium, but rather to sympathetic effects upon the atrial repolarization. The P-R and S-T segments are in "geometrical agreement."

If one takes an average duration of 0.30 second for the atrial electrical systole, and a cardiac rate of 80 cycles per minute, with a P-R interval of 0.16 second, it becomes evident that during approximately 0.14 second, the electrical activities of the atria and the

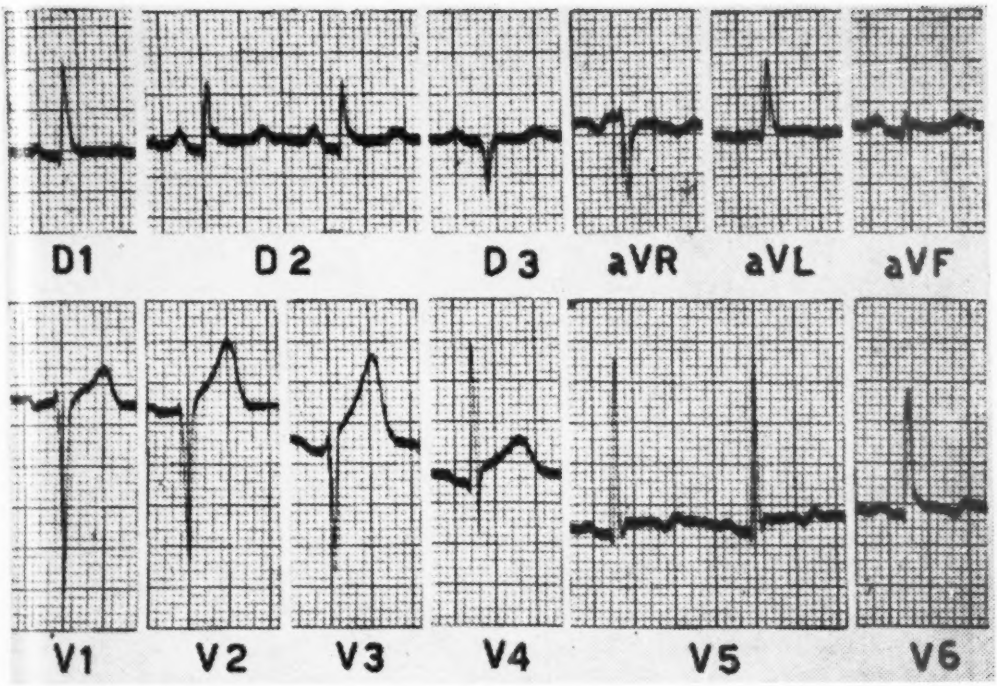

Figure 6

Electrocardiogram of a patient presenting clinical manifestations of acute coronary occlusion. There are no significant changes of the ventricular repolarization. However, the atrial J point and the P-R segment are markedly displaced in leads II and aV_R. The vector representing atrial "current of injury" is at −120°.

ventricles are superimposed. If one also subtracts the mean duration of the QRS complex, it becomes clear that the atrial repolarization is added to the ventricular repolarization for approximately 0.06 second (fig. 3). This fact gains extreme importance in electrocardiography, particularly when there are changes in the atrial repolarization that can simulate disturbances of the ventricular repolarization.[6]

Alterations of the Atrial Repolarization

The atrial repolarization may be modified in its spatial orientation or in its duration by different factors with resulting morphologic changes in the electrocardiogram (fig. 4). In a first group we have factors related to ischemic or necrotic phenomena, and conditions that act upon the atria by means of hypersympathetic stimulation (tachycardia, exercise, hyperthyroidism). These factors primarily affect the repolarization, and the changes they produce are considered as *primary alterations of the atrial repolarization.* Other factors affect the atrial activation (hypertrophy, dilatation, interatrial block), and repolarization secondarily. The changes produced are referred to as *secondary alterations of the atrial repolarization.*

We shall start by analyzing, separately, the modifications caused in the electrocardiogram by hypersympathetic activity.

Hypersympathetic Alterations of the Atrial Repolarization

The electrocardiographic changes produced by sympathetic effects in relation to the atrial repolarization are in general as follows: The

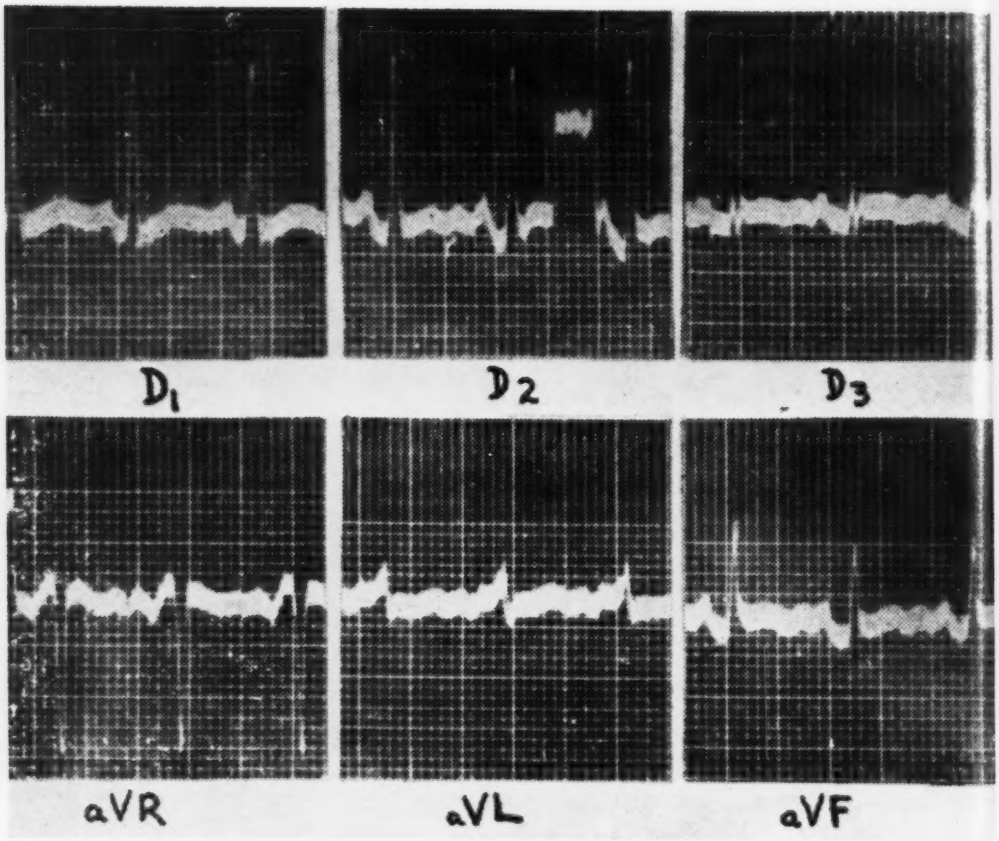

Figure 7

Electrocardiogram of a patient presenting wound of the right atrium produced by gunshot. The P-R segment is markedly displaced downward in leads II and aV_F. The vector representing atrial "current of injury" is at approximately −105°.

Ja point (P-PR junction) is maintained in the isoelectric line but the P-R segment is displaced markedly downward, showing an upward concavity, and the point of junction with the QRS complex is below the isoelectric line. At the same level lies the ventricular J point, whereas the S-T segment goes up fast, reaching the isoelectric line in the beginning of the T wave. It all appears as if the P-R and S-T segments were inscribed as arcs of a circumference with the same radius. Both displacements are in what may be termed "geometrical agreement" (fig. 5). Frequently the QRS complex is inscribed closer to the P wave than to the T wave, so that the center of the circumference formed by the P-R and S-T segments is localized to the right of the complex of ventricular activation (fig. 5). This gives rise to a greater displacement of the J point in relation to the point of junction, P-R-QRS (fig. 4*d*). Such changes definitely do not depend upon pathologic alterations of the atria, and so far we can only speculate upon its probable mechanism. It is possible that such anomalies are related to a faster propagation of the electrical phenomenon and to local metabolic changes with increase in the amplitude and reduction in the duration of

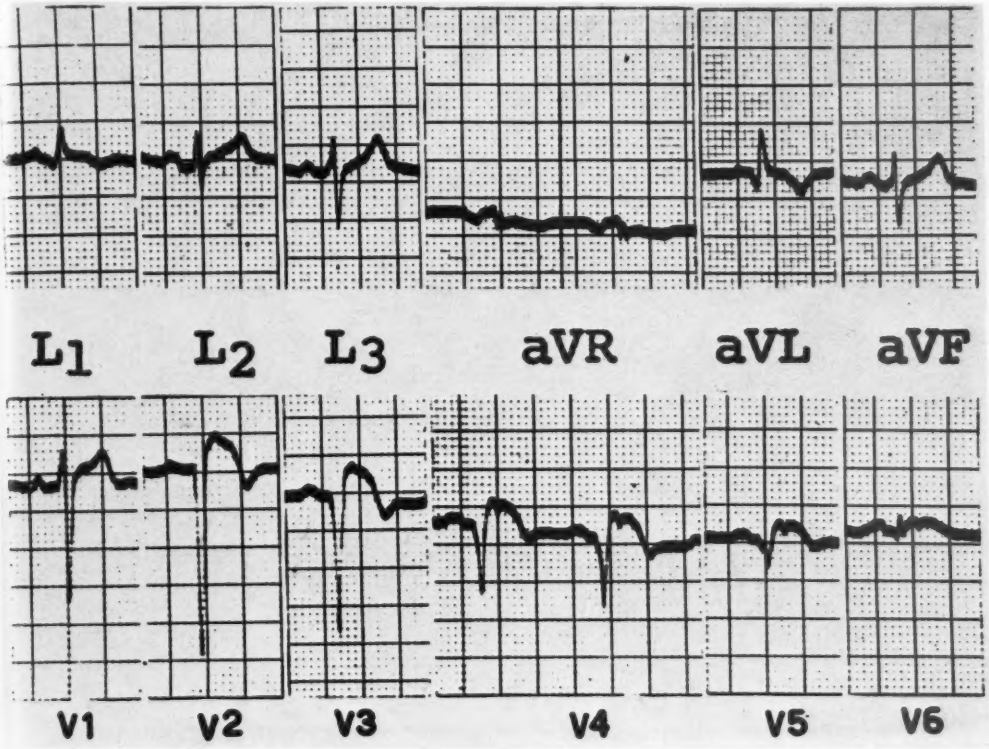

Figure 8

Acute extensive anterior infarction associated with atrial lesion. The P-R segment is displaced in leads II and aV_R. Note the notching in the S-T segment from V_4 to V_6 (superimposition of the Ta?).

all the complexes in the electrocardiogram.[4, 8] The inscription of the electrical phenomenon is made in such a way that the curve formed by the P-R segment, QRS complex, and S-T segment is shaped like an anchor (fig. 5). Therefore, in the interpretation of electrocardiograms we must always consider the possibility of sympathetic influences upon the atrial and ventricular repolarizations. For instance, a downward displacement of the S-T segment will not be suggestive of pathologic alteration if it is preceded by the same type of displacement of the P-R segment. The knowledge of the phenomena involving the atrial repolarization and the changes they may produce in the electrocardiogram acquires particular importance in the interpretation of the exercise tolerance test for the diagnosis of coronary insufficiency. After such a test, particularly if marked tachycardia is present, in normal individuals a downward displacement of the S-T segment may be inscribed with the same radius as the arc of the preceding P-R segment. When the ventricular complex is too close to the P wave (short P-R interval), it becomes more difficult to recognize the displacement of the P-R segment and, therefore, to observe if the arc formed by this P-R segment is in the same circumference with the arc inscribed by the S-T segment. In these cases the downward displacement of the S-T segment may be interpreted as meaning primary changes of the ventricular repolarization, thus leading to an incorrect diagnosis

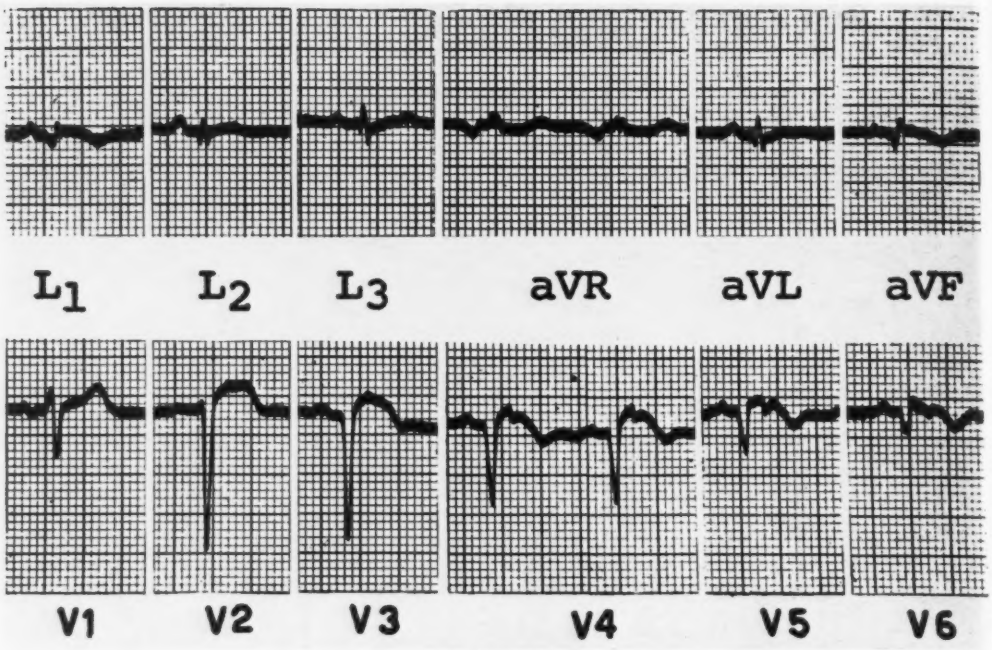

Figure 9

Electrocardiogram in same case as in figure 8, 20 days later. Improvement in the changes of the P-R segment indicating disappearance of the atrial lesion. However, the notching in the S-T segment from V_1 to V_6 is now more accentuated. We believe this is due to persistent ischemia.

of coronary insufficiency (fig. 5). The line of reference to be considered in the evaluation of a downward displacement of the S-T segment must be neither the supposedly isoelectric line that goes from the end of the T or U wave to the beginning of the P wave, nor the level of the preceding P-R segment, but the inclination with which this segment is inscribed. In so doing, we can establish with relative security the relationship between the arcs of the P-R and S-T segments. Only when all these factors are considered, can one safely analyze displacements of the S-T segments and see whether or not they agree with the arc formed by the preceding P-R. Thus, we may decide whether the S-T displacements are only due to alterations of the atrial repolarization or depend upon coronary insufficiency or other types of pathologic processes that disturb the repolarization of the ventricles. A myocardial ventricular lesion should only be diagnosed when there exists a disagreement greater than 0.05 mv. between the inscription of the segments;[8] in other words, when the P-R and S-T segments correspond to arcs of a circumference with different radius.[6] In cases of subepicardial ventricular lesions, the S-T is situated in a level above the P-R segment (figs. 4*c*, 4*e*, and 4*g*), and in cases of subendocardial lesions the S-T is located in a level below the P-R segment (figs. 4*b* and 4*f*).

Alterations of the Atrial Repolarization Produced by Ischemia and Structural Lesions

Processes that lead to structural lesions of ischemia of the atrial wall, such as infarcts, atrial wounds, and pericarditis, produce primary alterations of the atrial repolarization giving rise to changes in the S-Ta and in the Ta.[2, 4, 5, 12–14] Actually, necrosis consequent to infarction or a wound of the atrial wall affects

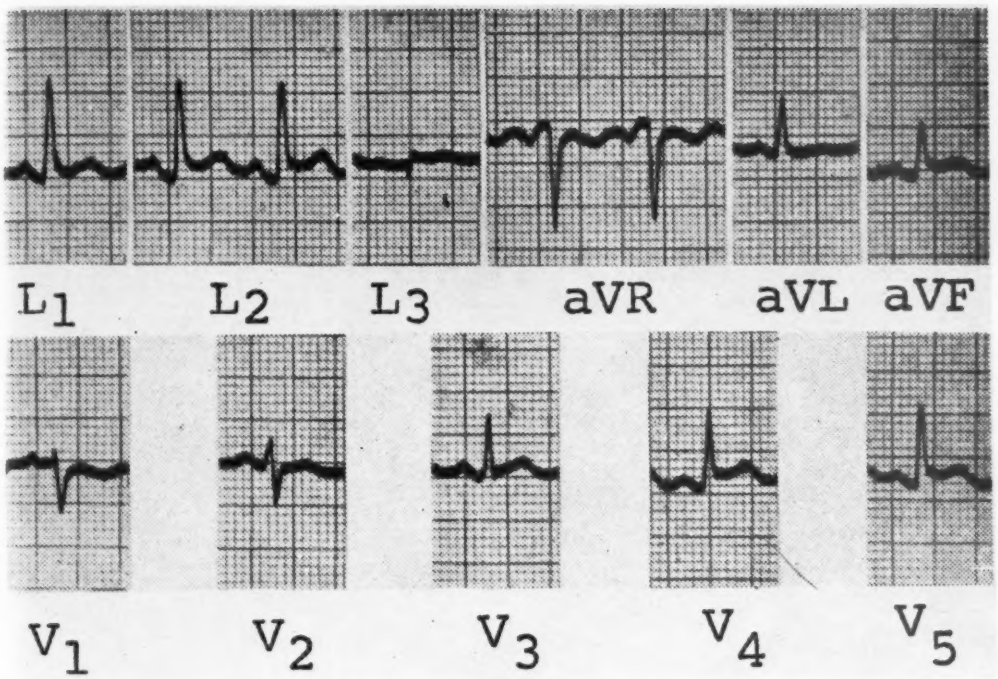

Figure 10

Acute pericarditis. Note the downward displacement of the P-R segment and the elevation of the S-T segment in lead II.

both the activation and repolarization of the atria. In the cases studied by us, however, we have noticed that the main changes are those concerning the Ja point and the P-R segment, which give rise to marked modifications of the S-Ta (figs. 6 and 7). In 1 patient with definite evidence of ventricular myocardial infarction, displacement of the P-R segment, particularly in leads II and aV_R, raised the suspicion of an associated atrial "current of injury" (fig. 8). In a tracing recorded 20 days later, the "current of injury" disappeared, although the ventricular infarction was still present and in evolution. The marked notching in the S-T segment in this case, particularly in leads V_2 through V_6 may be related to changes of the Ta as a consequence of persistent atrial ischemia (fig. 9).

Experimental lesions of the left atrium produce a positive displacement of the P-R segments in lead I, and lesions of the right atrium give rise to a negative displacement in this same lead.[1, 5] In both cases this segment is downward in leads II and III. Such observations have led us to conclude that in cases of left atrial lesions, the S-Ta vector is oriented approximately between –40 and –80 degrees, and in right atrial lesions between –100 and –140 degrees (figs. 6 and 7).

It is our opinion that careful analysis of the atrial repolarization is also of great value in the early diagnosis of pericarditis. Frequently, in the initial stages of pericardial inflammation, the subepicardial ventricular lesion is very mild. Concomitant tachycardia gives rise to downward displacement of the S-Ta. This downward displacement will balance to some extent the electrical effects of the ventricular lesion, which tends to produce upward S-T displacement. As a consequence

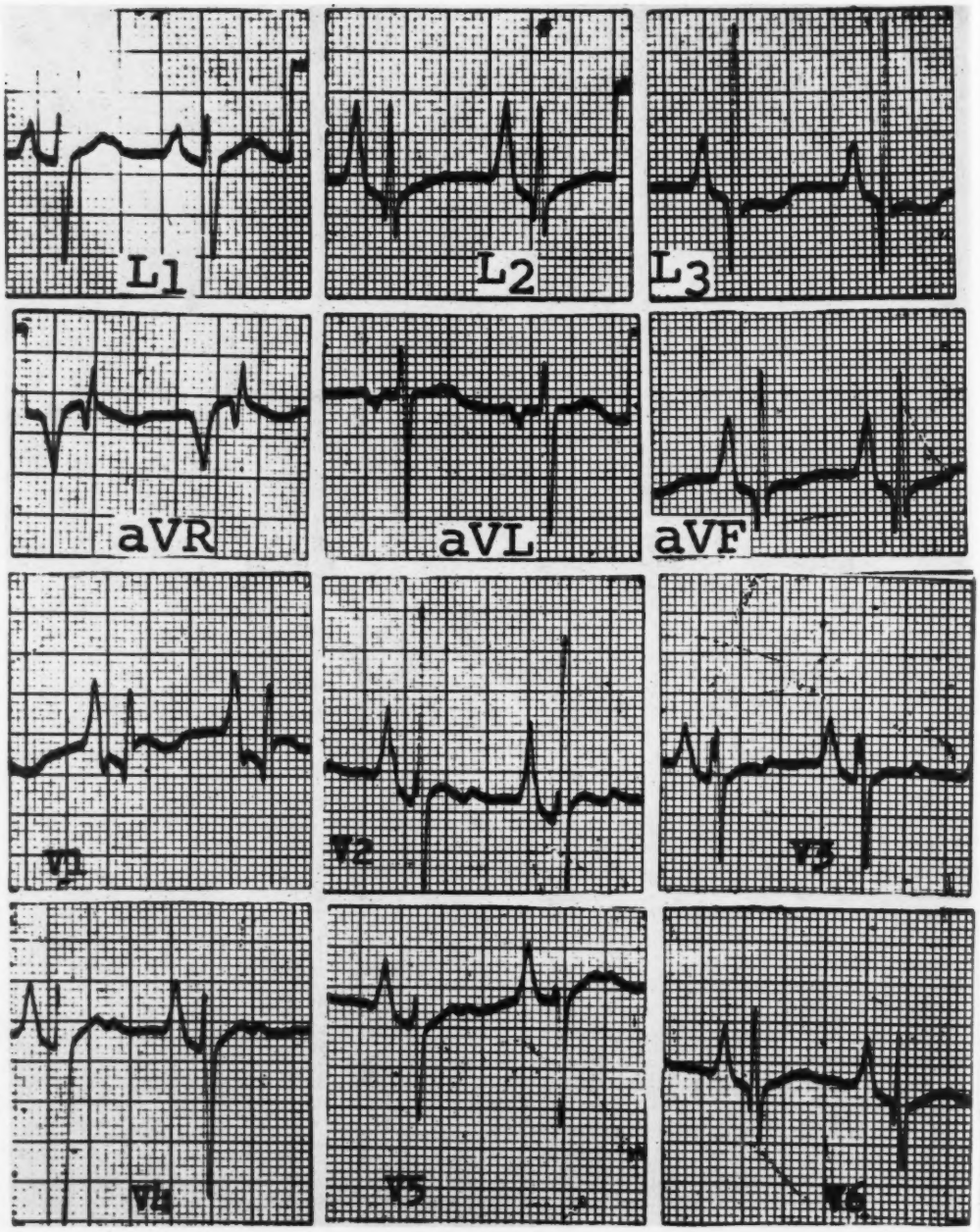

Figure 11

Cyanotic congenital heart disease. Tall peaked P waves and downward displacement of the Ja point. The P-R and S-T segments are in "geometrical agreement." This is a typical example of secondary alterations of the atrial repolarization.

of the balance between these 2 opposite vectorial forces, the S-T displacement will be less than usual, or, in some cases, will not be present at all. As long as there exists a clinical possibility of pericarditis, the existence of a downward P-R segment associated with an isoelectric or slightly upward S-T segment, would be very suggestive of subepicardial ventricular lesion (fig. 10).

Secondary Alterations of the Atrial Repolarization

The most frequent examples of secondary alterations of the atrial repolarization are found in cases of dilatation or hypertrophy of the atria, in which the repolarization is modified as a consequence of primary changes in the process of activation. In these cases the area of the S-Ta is increased proportionately to the increase of the area of the P wave, but these areas show an opposite polarity, that is, when P is positive, S-Ta is negative.

We must, therefore, assume that in such situations the downward displacement of the P-R, as a consequence of the changes of the S-Ta, may affect the S-T segment bringing it below the isoelectric line. Characteristically, in cases of secondary changes of the atrial repolarization, the Ja point is also displaced from its normal position, which suggests that the process of atrial repolarization starts before the process of activation is over (fig. 11). Changes imposed upon the ventricular S-T by secondary S-Ta and Ta alterations, however, show less magnitude than those produced by a sympathetic effect, and are associated with depression of the Ja point and increase in voltage or duration of the P wave.

Summary

A complete study of the electrical effects of the atrial repolarization is made, since it seems that such effects are often inadequately considered in the routine daily interpretation of electrocardiograms.

The alterations of the atrial repolarization are classified as follows: (1) primary, related to ischemia or injury of the atria, and hypersympathetic activity, (2) secondary, when appearing with modifications of the atrial activation, in cases of dilatation, hypertrophy, or intra-atrial block. The electrocardiographic changes produced by hypersympathetic activity are characterized by a P-PR junction (Ja) in the isoelectric line, descending P-R segment, depressed J point, and ascending S-T segment. The P-R and S-T segments have concordant deviations, which means that they behave as "arcs of a same circumference." The record of these electrical events is made in such a manner that the tracing can be morphologically compared to an anchor. An S-T depression has no pathologic significance whenever it is preceded by a concordant and symmetric P-R depression.

A myocardial injury is diagnosed only when the P-R and S-T segments are discordant, that is, when they correspond to "arcs of different circumference." An electrocardiographic exercise test is considered as negative, even in the presence of S-T depression, as long as this segment is inscribed with the same radius as that of the preceding P-R segment.

Other processes that act upon the atrial repolarization, such as atrial infarction, wounds, dilatation, hypertrophy, and pericarditis, are also analyzed, and their influence on the inscription of the ventricular repolarization is stressed.

Exact knowledge of the phenomena of atrial repolarization allows a more accurate interpretation of S-T displacements, and therefore is a safer diagnosis of the pathologic changes acting upon the ventricular repolarization.

Summario in Interlingua

Esseva facite un complete studio del effectos electric del repolarisation atrial, proque il pare que tal effectos es sovente considerate inadequatemente in le interpretation routinari diurne de electrocardiogrammas.

Le alterationes del repolarisation atrial es classificate sequentemente: (1) Primari, relationate a ischemia o trauma del atrios, e activitate hypersympathie, (2) secundari, quando manifeste con modificationes del activation atrial, in casos de dilatation, hypertrophia, o bloco intra-atrial. Le alterationes electrocardiographic producite per activitate hypersympathie es characterisate per un junction P-PR (Ja) in le linea isoelectric, un descendente segmento P-R, un deprimite puncto J, e un ascendente segmento S-T. Le segmentos P-R e S-T ha concordante devia-

tiones, i.e., illos se comporta como arcos del mesme circumferentia. Le registration de iste eventos electric es facite de maniera que le tracia pote esser comparate a un ancora. Un depression de S-T ha nulle signification pathologic quandocunque illo es precedite per un concordante e symmetric depression de P-R.

Un lesion myocardial es diagnosticate solmente quando le segmentos P-R e S-T es disconcordante, i.e., quando illos se comporta como arcos de differente circumferentias. Le electrocardiogramma de un test de exercitio es considerate como negative, mesmo in le presentia de un depression de S-T, si longo que iste segmento es inscribite con le mesme radius como le precedente segmento P-R.

Altere processos que age super le repolarisation atrial—infarcimento atrial, vulneres, dilatation, hypertrophia, pericarditis, etc.—es etiam analysate, e lor influentia super le inscription del repolarisation ventricular es sublineate.

Exacte cognoscentias del phenomenos de repolarisation atrial permitte un plus accurate interpretation de displaciamentos de S-T e resulta assi in plus fidel diagnoses del alterationes pathologic que age super le repolarisation ventricular.

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At the base of the study of management you will find the problem of authority. Not only are there different concepts of the true nature of authority, the differences can rise to serious trouble. If professional nursing first saw the light of day—or at least the light of Florence Nightingale's lamp—when the Victorian assumptions of masculine superiority and of the military theory of command were undisputed in a highly stratified society, then some growing pains were in store for nursing in a democracy, together with headaches for those who still postpone their study of the real nature of authority and how it relates to the effective management of human beings. I think that medical students and interns need particularly to reflect upon and learn the essentials of management and the importance of the consent of the governed in any sort of government. Success will but rarely attend the assumption that effective collaboration derives primarily from organization charts or stipulated chains of command, subordination, and hierarchies.—ALAN GREGG, M.D. *Challenges to Contemporary Medicine*. New York, Columbia University Press, 1956, p. 65.

ABSTRACTS

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Abstracters

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CORONARY ARTERY DISEASE

Rowell, N. R., and Smith, A. J.: Multiple Serial Enzyme Studies in Acute Myocardial Infarction. Brit. M. J. **2:** 459 (Sept. 19), 1959.

Upper limits of normal values for serum glutamic oxalacetic transaminase (SGOT) were 28 units; for serum glutamic pyruvic transaminase (SGPT), 21 units; for serum aldolase, 9.2 units; and for serum oxidase, 372 units as determined in 50 healthy adult individuals. Serial observations were then made during 28 episodes of uncomplicated acute myocardial infarction for at least 10 days. In all patients the SGOT was significantly elevated and this served as a reliable index of myocardial necrosis. Other enzymes were evaluated by this yardstick. Elevation of SGPT occurred in 82 per cent of the patients. The rise came a day later, lasted a day longer, and was of much smaller degree than the rise in SGOT. Serum aldolase rose rapidly in most patients, reached a peak in 2 or 3 days and then fell rapidly. A secondary rise occurred about 5 days after the initial peak. Serum oxidase levels rose gradually over the first 9 days, remained steady for a few days, and then fell to normal in most patients by 3 weeks. There was no good correlation with the rise in SGOT activity and serum oxidase was found to be normal with markedly elevated SGOT levels. There was no consistent correlation between the sedimentation rate, temperature, or the electrocardiogram, and the secondary rise in serum aldolase or the rise in serum oxidase. The authors reemphasize that the rise in serum levels of these enzymes is not organ specific, and liver disease in particular must be excluded. However, the pattern of the enzyme change is of help in localizing the disease. Thus, the rise of the SGOT to a lower peak than the SGPT, together with the secondary rise of the aldolase at about 5 days after its primary peak, and the increasing value of the serum oxidase seem to be characteristic of myocardial infarction. If the patient is seen several days after the acute infarct the transaminases may be normal but the diagnosis may be confirmed by finding the secondary peak of serum aldolase and by increasing the level of serum oxidase. Relative to prognosis, the quicker return of the serum aldolase level to normal may be of aid while the transaminases are still elevated. The peak of the aldolase in second infarcts is also more obvious because of this.

KRAUSE

Russek, Henry I.: Role of Heredity, Diet, and Emotional Stress in Coronary Heart Disease. J.A.M.A. **171:** 503 (Oct. 3), 1959.

The frequency of coronary heart disease in different parts of the world has been found to be related to the mode of life rather than to the racial structure or age composition of the population. In 91 of 100 patients with coronary heart disease, a period of prolonged emotional strain preceded the attack. In a comparable series of 100 patients with other diseases only 20 had undergone this type of strain. In coronary patients insecurity, frustration, and restlessness seemed to extend beyond the primary vocation into secondary occupations and leisure activity. Using the figures above, the author used a fraction of 91/20 or 4.6 per cent as a ratio of measuring the importance of occupational stress. The author found comparable ratios of 2.7 for diet, 2.0 for tobacco, 1.7 for heredity, 1.3 for obesity,

and 1 for lack of physical exercise in the relative importance of these factors in causing coronary heart disease. This suggests that the primary etiologic factor concerned with the leading cause of death in this country is our mode of life.

KITCHELL

Sanders, K.: Coronary-artery Disease and Obesity. Lancet **2**: 432 (Sept. 26), 1959.

The relation of obesity to coronary artery disease was reinvestigated. A group of 48 white hospital patients with recent onset of coronary artry disease were matched with a group of 52 healthy individuals selected at random from the National Health Service. Groups were matched for age, sex, nationality, domicile, and religion. Both patients and control subjects were measured for weight, height, and skinfold thickness. There was no evidence that the group with coronary artery disease was overweight. However, at any given weight, skinfold thickness was greater in the patients than in the control subjects, indicating a significantly increased mass of body fat and, presumably, a smaller active tissue mass.

KURLAND

Sigler, L. H.: Rupture of the Heart in Myocardial Infarction. Clinical and Pathologic Observations. Am. J. Cardiol. **5**: 14 (Jan.), 1960

The findings in 8 patients having myocardial infarction with cardiac rupture at the Adelphi Hospital in New York City were reviewed. These patients were observed during a recent 2-year period, which led the author to suspect that the frequency of rupture in acute infarction is higher than the reported incidence of 10 per cent. Rupture was believed to result from expansion of and hemorrhage into weakened myocardium, most commonly that of the anterior left ventricle. This complication developed principally in older patients and was ordinarily rapidly fatal; therefore surgical treatment was considered impractical. Prophylaxis was emphasized, namely, avoidance of excessive physical or emotional activity and of hypertension, especially during the first week of infarction when most of the ruptures occurred.

ROGERS

Talbert, J. L., Joyce, E. E., and Sabiston, D. C., Jr.: The Effect of Intra-Arterial Injection of Radiopaque Contrast Media on Coronary Blood Flow. Surgery **46**: 400 (Aug.), 1959.

Eleven mongrel dogs received a total of 133 intracoronary injections of 76 per cent Renografin (1.4 to 7.6 ml. per 100 Gm. of left ventricle), or 70 per cent Urokon (1.4 to 7.6 ml. per 100 Gm.), or physiologic saline (6.8 to 8.0 ml. per 100 Gm). When either of the contrast media was injected in the smaller quantities, comparable to those used clinically in coronary arteriography, the direct recording rotameter showed an immediate 5 to 10 per cent decrease in coronary flow. About 1 minute later coronary flow had increased 50 per cent; 30 seconds later flow had returned to control levels. These changes were attributed to a direct effect of the media on the coronary arteries, and were associated with moderate systemic hypotension for 1 to 2 minutes. After saline injection only a moderate transient flow increase occurred. These findings were considered not to contraindicate the judicious use of contrast media in coronary arteriography.

ROGERS

Thomas, W. A., Davies, J. N. P., O'Neal, R. M., and Dimakulangan, A. A.: Incidence of Myocardial Infarction Correlated with Venous and Pulmonary Thrombosis and Embolism. Am. J. Cardiol. **5**: 41 (Jan.), 1960.

The reports of similarly performed autopsies in 827 patients over 40 years of age at Makerere College in Uganda were compared with those performed in 2,237 patients at Barnes Hospital in St. Louis during the years 1951 to 1956. After age and sex matching, the incidence of myocardial infarction in the all-Negro Ugandans was 0.2 per cent, in the American Caucasians 22 per cent, and in the American Negroes 18 per cent. Venous thrombi were found in 2.4 per cent of Africans and in 22 per cent of each of the American groups. It appeared that myocardial infarction was rare among Ugandan Negroes and that this observation might be related to their seeming to have a diminished tendency to develop thrombosis.

ROGERS

Weber, A.: On Coronary Sclerosis, Especially in Physicians. Ztschr. Kreislaufforsch. **48**: 717 (Aug.), 1959.

Coronary sclerosis and myocardial infarction are especially common in physicians; the latter often appears at about 3 a.m., possibly because of hypotension at this time of night. When infarction appears during driving, the patient usually can stop the car without causing an accident. When the symptoms are not referred to the heart the electrocardiogram may be the only clue; even slight changes of the T wave and S-T segment are significant if they show progression. Coronary dilating drugs can prevent or postpone the appearance of myocardial infarction and by intravenous injection can cause sudden disappearance of pain. Digitalis should be used only in the presence of heart failure. These conclu-

sio s are based on 55 years of cardiologic experience by the author, to whom the entire issue of the journal is dedicated on the occasion of his eightieth birthday.

LEPESCHKIN

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Blifer, S., Kahn, M., Grishman, A., and Donoso, E.: Wolff-Parkinson-White Syndrome. A Vectocardiographic, Electrocardiographic and Clinical Study. Am. J. Cardiol. 4: 321 (Sept.), 1959.

Findings in 38 patients with anomalous atrioventricular excitation are presented. The ages ranged from 5 to 67 years: 22 were men. Other evidence of heart disease was lacking in 31; congenital heart disease was found in 4 and acquired heart disease in 3. Half the patients had noted palpitations. The patients were separated into 3 groups according to orientation of the delta wave in the horizontal plane. In the 11 individuals of group A, it was directed anteriorly in all and inferiorly and to the left in most. The 22 patients in group B had delta vectors oriented to the left in all and posteriorly and superiorly in most. The remaining 5 patients had atypical graphic findings. The delta portion of the QRS loop was usually oriented in the same direction as the remainder of the QRS sÊ loop. During anomalous atrioventricular excitation, the terminal as well as the initial QRS forces were altered, leading the authors to believe that the entire course of spread of the excitation wave was abnormal rather than that of the delta wave alone. The ability of this syndrome to mask other cardiographic abnormalities is emphasized, and methods for abolishing the anomalous conduction are described.

ROGERS

Clark, L. C., Jr., and Bargeron, L. M., Jr.: Detection and Direct Recording of Left-to-Right Shunts with the Hydrogen Electrode Catheter. Surgery 46: 797 (Oct.), 1959.

The use of a platinized platinum electrode capable of detecting hydrogen-containing blood is described as a method for recognizing left-to-right shunts. This technic does not require blood samples. The electrode, mounted at the tip of a cardiac catheter, develops a potential in the presence of blood that has been exposed to hydrogen in the lung following the administration of a breath of hydrogen. The method and results in over 40 catheterizations are outlined. In 1 patient with patient ductus arteriosus a small shunt was detected by the use of this technic, which was not revealed by the usual oxygen data.

SHEPS

Del Rio, R., Medrano, G., Rubio, V., Olea, J. P., Soin, J., and Sodi-Pallares, D.: Right Bundle Branch Block with Right Ventricular Hypertrophy. Am. J. Cardiol. 4: 294 (Sept.), 1959.

Thirty-eight patients having clinical and roentgenologic evidence of right ventricular hypertrophy were studied electrocardiographically by means of simultaneous right ventricular intracavitary and V_1 leads. Right bundle-branch block was found in 34 patients as indicated by a pre-intrinsicoid deflection time of 0.02 to 0.11 second in the intracavitary tracing. Electrocardiographic recognition of right ventricular hypertrophy in the presence of right bundle-branch block may be possible by analyzing all precordial leads, but the authors do not elaborate on this point. Right axis deviation of +120 to +180 degrees associated with right bundle-branch block is suggestive of right ventricular hypertrophy. Vectorcardiograms showing right bundle-branch block with and without hypertrophy are depicted.

ROGERS

NEWS FROM
THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7-9170

AHA Scientific Sessions Program

Program and abstracts of the 33rd annual Scientific Sessions of the American Heart Association are carried as a part II supplement to this issue of *Circulation*.

The Scientific Sessions will be held in Kiel Auditorium, St. Louis, from Friday, October 21 through Sunday, October 23. A total of 120 original scientific papers will be presented at sessions under sponsorship of the Association's Councils and during six simultaneous sessions on Clinical Cardiology.

This year for the first time a program for dentists, co-sponsored by the American Dental Association, is included. Scheduled for Friday afternoon, October 21, it is entitled "Management of Medical-Dental Problems in Patients with Cardiovascular Diseases." An all-day program for nurses, inaugurated successfully last year, has also been scheduled for Saturday, October 22.

Information relating to medical films, scientific and industrial exhibits and other features of the program are also included in the supplement.

AHA Annual Assembly Meeting

The AHA Assembly begins its Annual Meeting in St. Louis on Monday, October 24, and continues through Tuesday, October 25, in the Sheraton-Jefferson Hotel.

Delegates are invited to attend an open press conference on Sunday afternoon, October 23. The conference, on the subject of heart attacks, is under sponsorship of the Council on Community Service and Education. It will be moderated by Irvine H. Page, M.D., Director, Research Division, Cleveland Clinic Foundation, and former AHA President.

A report on recent achievements in medical and biological research will be presented by James V. Warren, M.D., Professor of Medicine and Chairman, Department of Internal Medicine, University of Texas Medical Branch, Galveston, at the opening general session on Monday morning.

Seven Assembly Panels will meet all day Monday to discuss the Association's programs and policies. The general Assembly convenes on Tuesday morning to discuss Panel recommendations and elect AHA officers and Board members. The Association's Annual Dinner will be held in the Sheraton-Jefferson Hotel on Sunday evening.

AHA Grant-In-Aid Applications Deadline is November 1

Applications for Heart Association grants-in-aid for the fiscal year beginning July 1, 1961 must be received by the Assistant Medical Director for Research at the AHA National Office, 44 East 23rd Street, New York 10, N. Y., not later than November 1, 1960. The deadline for submitting applications for Research Fellowships and Established Investigatorships was September 15.

All applications for grants-in-aid must be made on forms obtainable from the Association. Grants are made to nonprofit institutions in direct support of a particular investigator for a specific program of research under his direction. Awards are in support of research in the cardiovascular field or basic sciences for periods up to five years.

More AHA Affiliates Contribute To Supplement National Research

Additional contributions to supplement the AHA national research support program in

fiscal 1960-61 have been received from Heart Associations as follows:

Cayuga County (N. Y.) Heart Chapter, $500, in partial support of a grant for Paul N Yu, M.D., University of Rochester School of Medicine and Dentistry

Sullivan County (N. Y.) Heart Chapter, $2500, in partial support of a grant for Alvan R Feinstein, M.D., Irvington House, Irvington-on-Hudson, N. Y.

This brings to more than $84,000 the total received from Heart Associations for supplementary support of national research which had been approved but could not be financed for lack of funds.

T. Duckett Jones Award Presented

Rebecca C. Lancefield, Ph.D., Member and Professor, The Rockefeller Institute, has been presented the 1960 T. Duckett Jones Memorial Award in recognition of her "extensive and fruitful investigations of the biology of hemolytic streptococci."

Consisting of a $6500 stipend, the award was named for the late T. Duckett Jones, M.D., an authority on rheumatic fever. Before his death in 1954, Dr. Jones was active for many years in the Heart Association's Council on Rheumatic Fever and Congenital Heart Disease. He also served as an AHA Vice President and Board member.

The annual award is made possible by contributions to the T. Duckett Jones Memorial Fund which are matched by the Helen Hay Whitney Foundation.

Meetings Calendar

October 21-23: American College of Cardiology, 9th Interim Meeting, St. Louis. Philip Reichert, American College of Cardiology, 350 Fifth Avenue, New York, N. Y.

October 21-25: American Heart Association, Annual Meeting and Scientific Sessions (October 21-23), St. Louis. American Heart Association, 44 East 23rd Street, New York 10, N. Y.

October 31-November 2: Association of American Medical Colleges, Hollywood Beach, Fla. Ward Darley, 2530 Ridge Ave., Evanston, Ill.

October 30-November 4: American Public Health Association, San Francisco. B. F. Mattison, 1790 Broadway, New York 19, N. Y.

November 3-4: International Conference "Muscle as a Tissue," Philadelphia. K. Rodahl, Lankenau Hospital, Philadelphia 31, Pa.

November 28-December 2: American Medical Association, Clinical Meeting, Washington, D. C. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Ill.

November 30-December 3: Canadian Heart Association and National Heart Foundation of Canada, Toronto. J. B. Armstrong, 501 Yonge Street, Toronto 5, Canada.

1961

January 9-12: White House Conference on Aging, Washington, D. C. Miss Esther C. Stamats, Department of Health, Education and Welfare, Washington 25, D. C.

February 8-11: American College of Radiology, Chicago. W. C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill.

March 13-16: National Health Council, New York. Philip E. Ryan, 1790 Broadway, New York 19, N. Y.

March 20-24: American Surgical Association, Boca Raton, Fla. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 10-14: American Physiological Society, Atlantic City. Ray G. Daggs, 9650 Wisconsin Ave., Washington 14, D. C.

April 17-20: American Academy of General Practice, Miami Beach. Mac F. Cahal, Volker at Brookside, Kansas City 12, Mo.

April 24-26: American Association for Thoracic Surgery, Philadelphia. Miss Ada Harvey, 7730 Carondelet Ave., St. Louis 5, Mo.

April 30: American Federation for Clinical Research, Atlantic City. James E. Bryan, 250 W. 57th Street, New York 19, N. Y.

June 26-30: American Medical Association, Annual Meeting, New York. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Ill.

November 16-18: International Symposium "Etiology of Myocardial Infarction," Detroit. Thomas N. James, Henry Ford Hospital, Detroit 2, Mich.

Abroad

October 19-23: Symposium on Rheumatic Diseases, Ixtapan, Mexico. General Tours, Inc., 595 Madison Ave., New York 22, N. Y.

1961

August 22-25: International Pharmacological Meeting (First) Stockholm. A. Wretlind, Karolinska Institutet, Stockholm 60, Sweden.

September 4-7: International Congress on Rheumatology, Rome. Prof. C. B. Ballabio, Clinica Medica Generale, Via F. Sforza 35, Milano, Italy.

1962

October: Fourth World Congress of Cardiology, Mexico City. I. Chavez, Ave. Cuauhtemoc, 300, Mexico, D. F.

THE COUNCIL ON ARTERIOSCLEROSIS OF THE AMERICAN HEART ASSOCIATION

The American Society for the Study of Arteriosclerosis

PROGRAM AND ABSTRACTS

OF THE FOURTEENTH ANNUAL MEETING

SHERATON JEFFERSON HOTEL, OCTOBER 19 AND 20

AND KIEL AUDITORIUM, OCTOBER 21, 1960

St. Louis, Missouri

(All papers except the Addresses will be limited to 10 minutes for presentation plus 5 minutes for discussion.)

WEDNESDAY MORNING OCTOBER 19, 1960

CRYSTAL ROOM

Sheraton Jefferson Hotel

8:00 a.m. Registration

Forrest Kendall, Presiding

9:00

1. Absence of Lipoprotein Lipase in Human Adipose Tissue Extracts

Hyman Engleberg. From the Cedars of Lebanon Hospital, Beverly Hills, California

Human subcutaneous and mesenteric adipose tissue was obtained at surgery and quickly frozen. Extracts were prepared according to the method of Korn and Quigley. Lipoprotein lipase activity was evaluated by determining glycerol release using activated coconut oil and human low density lipoproteins as substrates.

In all, 6 pools of human tissue extracts, obtained from 15-20 individuals, were tested. No evidence of lipolysis was found in 5 and there was possibly trace activity in one which was so slight that the effects of inhibitors could not be evaluated. On the other hand chicken adipose tissue, extracted by the same method, gave excellent activity. These results afford evidence that lipoprotein lipase is not present in substantial amounts in human adipose tissue.

9:15

2. Factors Which Influence the Denaturation of Serum β-Lipoproteins

Toshiro Nishida, Hideo Tsuchiyama and Fred A. Kummerow. From the Department of Food Technology, University of Illinois, Urbana, Illinois

β-Lipoproteins may serve as a possible initiating step in the formation of bound lipid in the involved portions of human aortas. In the present study the *in vitro* formation of lipohydroperoxide in β-lipoprotein and the subsequent degradation of the lipoprotein was followed by means of chemical, spectrophotometric, electrophoretic and ultracentrifugal analyses.

The results indicated that hematin compounds greatly accelerated the formation of lipohydroperoxide in isolated β-lipoproteins which resulted in rapid denaturation of the β-lipoproteins. In an *in vivo* study the intravenous injection, into chicks which had been kept on a low vitamin E diet, of as small an amount as 10 mg. of the hydroperoxide of methyl linoleate emulsified in serum caused petechial hemorrhages in the cerebellum. The intravenous injection of an emulsion of reduced methyl linoleate hydroperoxide, a long chain keto acid, or fresh methyl linoleate did not cause hemorrhage. As it is recognized that thrombosis or hemorrhage in the arterial wall is often associated with atherosclerosis, it is possible that in some cases lipohydroperoxides may initiate such phenomena. The chemical, physical and biological nature of peroxidation and the factors which accelerate or prevent denaturation of β-lipoproteins will be discussed.

9:30

3. Tocopherol in the Atherosclerotic Human Aorta

Eugene C. McCormick and Robert H. McCluer. From Conway Springs, Kansas and Columbus, Ohio

Tocopherol would be expected to be deposited in atheromas, as this lipid antioxidant has been shown in this laboratory to be transported principally by the atherogenic low density lipoproteins.

In the present study tocopherol in the free, ester and quinone forms was determined in normal and atherosclerotic aortas. Over 85 per cent of the Emmerie-Engel reducing substance in the nonsaponifiable fraction was demonstrated to be tocopherol or tocopherol quinone by spectral analysis of chromatographically purified samples. The total tocopherol content of aortas was 2 to 3 mg./Gm. wet tissue in normal and up to 16 mg./Gm. in severely atherosclerotic aortas. The tocopherol to cholesterol ratio was similar in normal and atherosclerotic aortas, as well as in isolated atheromas, the mean ratio being 0.0046. This ratio is close to that found in normal plasma. The per cent quinone (12 to 36) is also close to that of plasma. No tocopherol ester was found. Tocopherol, measured by its antioxidant capacity in terms of β-carotene half-life in the presence of excess hydroperoxide, was 97 to 104 per cent of the chemically assayed tocopherol content. There was no indication of tocopherol toxicity in the aortic lipid extracts.

In view of the tocopherol/cholesterol ratio, carotenoid/cholesterol ratio, per cent quinone and antioxidant capacity of atherosclerotic aortas, there appears to be adequate tocopherol in atheromas to prevent lipid peroxidation. Therefore, the reported existence of lipid peroxides in atheromas is inconsistent with the lipid antioxidant role of tocopherol.

9:45

4. Relative Deficiency of Protein Bound Phosphatidyl Choline and Lysophosphatidyl Choline in Human Arteriosclerosis

L. O. Pilgeram, W. F. Prigge and T. C. Lee. From the Arteriosclerosis Research Laboratory, St. Barnabas Hospital Research Foundation and the Department of Physiology, University of Minnesota School of Medicine, Minneapolis 4, Minnesota

Antecubital vein blood was drawn from healthy 8 hour fasted subjects of age 19 to 54 years and from subjects who had recovered from a myocardial infarction or a cerebral vascular accident for a period of not less than 6 months and who were without anticoagulant therapy. The age range for the pathologicals was 34 to 61 years. Blood samples were processed immediately after withdrawal.

Phosphatides, which were quantitatively extracted from the alpha and beta lipoproteins, were resolved by silicic acid paper chromatography and quantitatively determined by analyses of phosphorus content.

Results indicate the presence of lysophosphatidyl choline, sphingomyelin, phosphatidyl choline, phosphatidic acid (provisional identification) and an immobile, R_f 0.0, unidentified phosphorus containing factor(s) along with cholesterol, cholesterol esters, triglyceride, and fatty acids in each alpha and beta fraction. The percentage changes of the pathological with respect to the normal in the alpha lipoprotein are: Spot R_f 0.0 (+59, $p < .004$), lysophosphatidyl choline (+ 14.9, not significant), sphingomyelin (+53.7, $p < .004$), phosphatidyl choline (+5.1, not significant), and phosphatidic acid (+61.2, $p < .002$). Beta lipoprotein: Spot R_f 0.0 (+140.8, $p < .001$), lysophosphatidyl choline (+33.7, $p > 0.30$, not significant), sphingomyelin (+53.5 $p < .04$), phosphatidyl choline (+37.2, $p = .07$), and phosphatidic acid (+59.5, $p = .03$).

Sphingomyelin and phosphatidic acid show no change in the alpha-beta distribution ratio in passing from a normal to an arteriosclerotic condition while, in contrast, lysophosphatidyl choline, phosphatidyl choline, and spot R_f 0.0 distribution ratios are significantly reduced.

Alpha phosphatidyl choline and alpha lysophosphatidyl choline are unable to maintain an increase in concentration proportionate to the observed increases of the other phosphatides. The tendency

appears to a lesser degree for beta phosphatidyl choline and lysophosphatidyl choline. This peculiar change also shows up in the distribution of phosphorus where only phosphatidyl choline and lysophosphatidyl choline possess a relative decrease in passing from the normal to the pathological state.

10:00

5. Effect of Bile Acids on the Fecal Excretion of Accumulated Tissue Cholesterol

William T. Beher, William L. Anthony, Gizella D. Baker, and John R. Caldwell. From the Edsel B. Ford Institute for Medical Research, Henry Ford Hospital, Detroit 2, Michigan

Dietary bile acids have been shown to influence the rate of mobilization of accumulated cholesterol in mice and rats. Two of these substances, cholic and hyodeoxycholic acids, had definite and opposite effects on the mobilization of mouse liver cholesterol. Cholic acid decreased the excretion rate, while hyodeoxycholic acid strikingly increased the rate and reversed the effect of cholic acid. Since cholesterol excretion can proceed via two pathways: (a) fecal sterols or (b) oxidation to bile acids and excretion; we have determined the effects of cholic and hyodeoxycholic acids on the rate and pattern of cholesterol excretion in the mouse.

Mouse tissue cholesterol was elevated by feeding cholesterol-4-C^{14}. The mice were then divided into 3 groups: I, control; II, cholic acid treated; and III, hyodeoxycholic acid treated. The feces were collected at intervals for 20 days, and the fecal steroids extracted and fractionated. The amount of each fraction and its C^{14} activity were determined.

In comparison with control animals, cholic acid depressed total *steroid* excretion, the depression occurring in the bile acid fraction; while the excretion of fecal *sterols* remained relatively unaltered. On the other hand, hyodeoxycholic acid greatly increased total *steroid* excretion. In this case the increase was in the *sterol* fraction, while bile acid excretion was depressed.

10:15

6. In Vitro Exchange of Cholesterol Between Lipoprotein Fractions

Paul S. Roheim, David E. Haft, Abraham White and Howard A. Eder. From the Albert Einstein College of Medicine, New York 61, New York

Previous studies in this laboratory have indicated that phospholipids exchange *in vitro* between different lipoprotein fractions. It has also been shown that free cholesterol is readily exchanged between red cells and plasma and that esterified cholesterol is exchanged to a considerably lesser degree (Hagerman and Gould). In order to study the exchange of cholesterol *in vitro* between plasma lipoprotein fractions, labeled lipoproteins were prepared by perfusing isolated rat livers with acetate 1-C^{14} or mevalonic acid 2-C^{14}. Lipoproteins of labeled and unlabeled plasma were separated by ultracentrifugal flotation into low density (D $<$ 1.063) and high density (D $>$ 1.063) lipoprotein fractions. Labeled low density lipoproteins were mixed with unlabeled high density lipoproteins, and labeled high density lipoproteins were mixed with unlabeled low density lipoproteins. After incubations at various intervals and at 4° and 37° the lipoproteins in the mixtures were separated again and the specific activity of cholesterol was determined in the different fractions.

Complete equilibration of free cholesterol occurred within a few hours at 37° and there was already appreciable exchange within minutes after mixing. Very little exchange of esterified cholesterol was observed even after 24 hours at 37°.

In another series of experiments cholesterol labeled chylocimrons, obtained from intestinal lymph of rats gavaged with cholesterol-4-C^{14}, were incubated with unlabeled plasma. After incubation the chylomicrons and the different lipoprotein fractions were separated and the exchange of cholesterol was determined. Again there was complete equilibration of free cholesterol between the lipoprotein fractions and the chylomicrons. The exchange of esterified cholesterol was so small as to appear insignificant.

10:30-10:45 Intermission

10:45

7. The Significance of Abnormal Lipid Patterns in Familial Hypercholesterolemia with Xanthomatosis

Teofil Kheim, William B. Kountz, Gelson Toro and Philip G. Ackermann. From the Division of Gerontology, Washington University, St. Louis 39, Missouri

A hypercholesterolemic family with xanthomatosis composed of 69 members has been studied for a year. Forty-six members received repeated clinical and laboratory examination. Hospital or autopsy record or information about 14 additional members were secured. Sixteen of the examined blood relatives had an average of 478 mg. per cent serum cholesterol (range 348-635). Nine of the hypercholesterolemic individuals had angina pectoris and 5 of them a history of myocardial infarction. The coronary disease in the parent generation started in their sixth decade, in the F

generation between 26 and 38 years. The F_2 generation (2-20) is up to now apparently free from heart symptoms.

In the hypercholesterolemic male members of the F_1 generation, the mean relative concentration of alpha-l lipoproteins was 5.6 per cent (range 4-6), beta 86.4 per cent (80-92), the absolute values being 28 mg. per cent (24-32) and 375.4 mg. per cent (324-547), respectively. The departure from normal of the zone electrophoretic lipoprotein pattern in normocholesterolemic blood relatives would seem to be the best indicator for the detection of heterozygotes in a hypercholesteroiemic family.

Neither the elevated cholesterol levels nor the abnormal lipid patterns could be influenced by a long-term rigid corn oil diet with low saturated fat content or by cholesterol-lowering agents.

11:00

8. The Analogy Between Early Atherosclerosis and Encrustations in Extracorporeal Circulations

Edmond A. Murphy, Harold C. Rowsell, Harold G. Downie, Gerald A. Robinson and James F. Mustard. From the Ontario Veterinary College, Guelph; Sunnybrook Hospital, Department of Medicine, University of Toronto, Toronto 12, Ontario, Canada

A study of the earliest lesions of atherosclerosis may make it possible to distinguish between initial and complicating mechanisms. Lesions believed to be the precursors of atherosclerosis occur typically at the aortic valve, the ductus scar, laterally and distally to small vessel orifices characteristically sparing the proximal lip, and on the lateral aspects of bifurcations. At first floccular, they may later coalesce into transverse ribs or longitudinal streaks. They are frequently rich in lipids and acid mucopolysaccharides.

The possible role of encrustation and the importance of hydraulic factors in localizing nascent atherosclerosis have been studied in siliconed plastic or brass models connected to the circulations of pigs for periods of from 15 to 30 minutes. The sites and patterns of deposits about bifurcations and orifices were strikingly similar to those of early atherosclerosis. The initial deposits in the models have been identified as platelet thrombi by histochemical, fluorescent antibody and isotope tagging techniques. Only at later stages are fibrin and red cells deposited. The platelet deposits stained with fat stains macroscopically unless much fibrin was present. Furthermore, staining was intensified by simultaneous intravenous infusion of fat.

In these mechanical systems, the effects of the biophysical properties of the arterial wall are eliminated. Nevertheless, a very close analogy both topographical and histochemical has been demonstrated between the deposits formed and early atherosclerosis. This suggests a plausible hypothesis—that an important early mechanism in atherogenesis is platelet deposition, influenced by hydraulic factors.

11:15

9. Fibrinolytic Activity of Arterial Tissues

Jack Lieberman, and Frederick Kellogg. From Long Beach, California

A study of the plasminogen activator within the walls of arteries was undertaken to investigate the possibility that an intrinsic deficiency in fibrinolysis may predispose to intravascular-fibrin deposition as the initial stage of atherosclerosis. Plasminogen activator was assayed by means of a fibrin-plate technic. Activity was expressed as the product of two perpendicular diameters through the area of lysis which results from the application of a 5 mm. disk of arterial tissue to the fibrin plate for 24 hours at 37° C.

Plasminogen-activator activity was found localized to the adventitial layer in almost all vessels studied. Enzyme activity appeared incapable of penetrating the intact intima, although minimal activity was detected within areas of erosion accompanying moderate to marked atherosclerosis. In a study of fetal aortas a maturation delay in the appearance of the enzyme was evident so that fetuses less than 2,000 Gm. in weight lacked activity. In adult males, activity of the aorta appeared fairly constant in all age groups, although somewhat higher levels were observed in those over 60. Females differed in that activity was higher at ages under 60, but dropped to comparable male levels at higher ages.

Variation in the level of enzyme activity was also observed between the different arteries studied. The basilar artery showed the lowest activity (242 ± 282 units, $n = 26$) < pulmonary artery (316 ± 221, $n = 29$) < renal artery (638 ± 276, $n = 23$) = abdominal aorta (716 ± 383, $n = 130$) = arch of aorta (745 ± 448, $n = 142$) = coronary artery (746 ± 524, $n = 106$). A difference between the coronary arteries of males and females also was seen: males: 642 ± 467 units, $n = 53$, females: 836 ± 557 units, $n = 53$. No correlation was observed between the presence of atherosclerosis within the aorta or coronary arteries and the level of enzyme activity.

From these data it would appear difficult to assign a role for the pathogenesis of atherosclerosis to the plasminogen activator of arterial tissues other than that related to its customary absence from the vascular intima. The differences in

enzyme activity observed between males and females are of interest, but their importance cannot be assessed at this time.

11:30

10. The Thromboplastin Activities of Human Arterial and Venous Tissue

John E. Kirk. From the Division of Gerontology, School of Medicine, Washington University, St. Louis 39, Missouri

Duguid's theory concerning the pathogenesis of atherosclerosis has received increasing attention in recent years. In order to provide quantitative data on the thromboplastin activity of human vascular tissue, determinations were made of the enzyme activities of 15 samples of the aorta, pulmonary artery, and inferior vena cava. For comparative purposes, both normal and arteriosclerotic portions of the aorta were included in the study. The thromboplastin measurements were made by a modification of Astrup's procedure with the use of reconstituted lyophilized human plasma. The activities of the vascular tissue samples were compared with those of homogenates of human brain tissue and were expressed in percentage of the brain tissue activity.

The average thromboplastin activities found for the various layers of the aorta were: normal intima, 3.6; arteriosclerotic intima, 2.4; normal media, 2.5; arteriosclerotic media, 2.6; adventitia, 1.4. These results do not indicate a tendency for the activity of the arteriosclerotic tissue to exceed that of the normal tissue. The average values recorded for the vena cava layers were of the same order of magnitude as those observed for the aorta (intima, 3.3; media, 2.6). In contrast to this, significantly lower thromboplastin values were found for the intima and media samples of the pulmonary artery, the mean values being, respectively, 0.9 and 1.6.

11:45

11. Platelet Turnover, Coagulation and Atherosclerosis

James F. Mustard, Edmond A. Murphy and Gerald A. Robinson. From the Sunnybrook Hospital, Department of Medicine, University of Toronto and Ontario Veterinary College, Guelph, Canada

Previous studies have shown that tests of the early stages of clotting are more active in atherosclerotic patients than in controls; in controls with a positive family history, the tests are more active than in those with a negative family history. It is important to determine whether these differences *in vitro* reflect real differences *in vivo*. A method of doing this is to study the turnover of some factor consumed in coagulation such as platelets. Platelets participate in the early stages of clotting, are the earliest components of a thrombus and probably play a part in atherogenesis, if encrustations are an important mechanism. Platelet turnover can be investigated by labelling them *in vivo* with P^{32}-labelled di-isopropyl fluoro phosphonate.

Thirty-one subjects with a history of atherosclerotic vessel disease, but no recent catastrophe were compared with 43 controls. The mean platelet survival was significantly shorter in the atherosclerotic group than in the controls whether or not an age correction was used ($p < .01$). Furthermore, among the control patients those with a positive family history had a shorter mean platelet survival than those with a negative history. Similar results were obtained if platelet turnover (platelet count/mean platelet survival) was considered instead. Furthermore, fair correlations were found with the *in vitro* clotting tests.

It is concluded that subjects with clinical complications of atherosclerosis and controls with a positive family history have increased activity of the clotting mechanism as manifested by *in vitro* and *in vivo* tests of platelet function.

WEDNESDAY AFTERNOON

Crystal Room

1:45-3:00 Business Meeting and Presidential Address: Forrest E. Kendall

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Robert H. Furman, Presiding

3:00

12. Histochemical Studies in Coronary Atherogenesis

Frederick T. Zugibe and Kenneth D. Brown. From the Veterans Administration Hospital, Downey, Ill., and Department of Biochemistry, Northwestern University Medical School, Chicago, Ill.

A histochemical study of human coronary arteries ranging from fetuses to 70 years of age has been made, utilizing new histochemical and histological technics developed in our laboratory. These include a new carbowax method which produces sections with minimal lipid loss, enables routine stains to be applied to adjacent sections, and permits observations of both lipid and acid mucopolysaccharides (AMP) on the same tissue sections. In addition, new methods have been utilized to

identify and localize the individual AMP histochemically.

The following is a preliminary report of our observations: There is no relationship between AMP and lipid in respect to staining intensity and/or distribution in any of the age groups studied.

Lipid was absent in the fetuses but was frequently observed in infants and young juveniles. This lipid was present within endothelial cells or as isolated droplets in the intima. In the older juveniles and adults, lipid was frequently observed within the fiber as previously reported in the aortas and cerebral arteries.

Fragmentation, fraying and/or reduplication of the internal elastic membrane was present in all of the groups studied. There was an increase in AMP in association with the intima but this AMP in the fetuses, infants and juveniles was essentially chondroitin sulfate A and was either associated with fine collagen fiber or with the absence of collagen. In general, the ratio of chondroitin sulfate B to chondroitin sulfate A and/or chondroitin sulfate C increases with age and/or with severe changes in the internal elastic membrane. Concomitantly, there is an increase in the ratio of coarse collagen to fine collagen. This close association suggests a reinforcement mechanism to strengthen the arterial wall.

A comparison of these studies with our previously reported observations on aortas and cerebral arteries will be given. In addition, the significance of these findings will be discussed.

3:15

13. A Histoenzymatic and Histochemical Study of Human and Experimental Atherogenesis

I. Ernest Gonzalez. From the University of Alabama Medical Center, Department of Pathology, Birmingham, Ala.

In a previous study relating to canine atherogenesis following I^{131} administration and cholesterol feeding Gonzalez and co-workers presented evidence suggesting that substances containing 1-2 glycol linkages were intimately associated with the development of early aortic lesions.

Subsequent studies relating to human atherogenesis indicate that acid phosphatases and non-specific esterase activity are closely associated with intimal proliferation and the development of atherosclerotic lesions. Lipid-laden cells first noted in the intima of developing lesions exhibit even greater acid phosphatase and non-specific esterase activity. Other histoenzymatic studies for fat peroxides and histochemical studies for fatty aldehydes and hydroxy fatty acids suggest that Schiff-positive groups may represent intermediate stages in the oxidation of lipids found in the "fatty streaks" and "fibrous plaques" developing in the arterial bed.

Atheroma, in part, represent products of oxidizing lipids, possibly unsaturated phosphatides or unsaturated fatty acids of high molecular weight, which may not stain with conventional fat soluble dyes.

These in situ histoenzymatic studies point out the need for further studies relating to the focal atherosclerotic lesion.

3:30

14. A Non-Atheromatous Vascular Lesion Causally Related to Diabetes Mellitus

Herman T. Blumenthal, Sidney Goldenberg, and Morris Alex. From the Institute of Experimental Pathology, The Jewish Hospital, St. Louis, Mo.

A vascular lesion will be demonstrated consisting primarily of endothelial proliferation with a laying down of fine PAS positive, colloidal iron negative fibrils. This lesion will be shown in the placenta, heart, amputated extremities, eye, kidney and brain of diabetic subjects. Statistical data will also be presented showing that this lesion occurs with a significantly greater frequency in diabetic than in non-diabetic subjects. The pathogenic development of this lesion will be traced and compared with ordinary arteriosclerosis in order to show that while the former is largely a proliferative endarteritis, the latter develops through a series of non-cellular connective tissue reactions. Comparisons will also be made between the "diabetic" lesion and those occurring in various hypersensitivity phenomena in order to draw inferences as to etiology. In addition to the proliferative character of the vascular lesions, such associated changes as fibrinoid degeneration, giant cell formation, etc. will be demonstrated in order to further support the concept that there is a causally related vascular disease in diabetes which is probably immunogenic in origin.

3:45

15. Electron Microscopy of Human Atherosclerotic Lesions

Henry C. McGill, Jr., Jack C. Geer, and Jack P. Strong. From the Louisiana State University School of Medicine, New Orleans, La.

Coronary and aortic atherosclerotic lesions from 13 human cases from 7 to 56 years of age have been examined by electron microscopy of postmortem tissue, with emphasis on the uncomplicated fatty streak. The lipid in small, presum-

ably early fatty streaks in young individuals is predominantly within smooth muscle cells of the intima and inner media. Extracellular lipid is observed only in association with large amounts of intracellular lipid and morphologic evidence of cytoplasmic degeneration. Both intracellular and extracellular lipid occurs in a variety of structural forms. The proportions of different forms in simple fatty streaks varies widely from lesion to lesion. Although the chemical identity of each form is not known, the varying morphology is probably based on differing chemical composition. These observations indicate that the lipid in fatty streaks forms first in the cytoplasm of smooth muscle cells, and that its chemical composition is both complex and variable. Further accumulation of lipid progresses to form larger fatty streaks with foam cells; or cellular degeneration may occur, leading to extracellular lipid. Extracellular lipid is possibly the stimulus for collagen deposition and the subsequent formation of the fibrous plaque.

4:00

16. Pathogenesis of Atheroma

Robert H. More and M. Daria Haust. From the Department of Pathology, Queen's University, Kingston, Ontario, Canada

Material for this study consisted of 130 sections selected from 1300 sections of arteriosclerotic lesions from 150 aortas and the coronary arteries of 100 hearts. The 130 sections chosen, represented various stages of atheroma formation and lesions believed to be the precursors of atheroma.

In these sections fibrous plaques as previously reported, developed out of organization of mural thrombi and intimal inflammatory exudates. In some of these areas of incomplete organization lipophages were adjacent to remnants of fibrin and fibrinoid. In older lesions the fibrinous material decreased and in some of these there was an increase in lipid material, both intracellular and extracellular, with formation of classical atheroma.

In these studies it was not possible to determine what factors determine whether or not organization would result in atheroma formation or just fibrous plaque formation. Our observations, do, however, warrant the conclusion that the atheromatous component of at least some arteriosclerotic lesions results from lack of organization of either thrombi and/or exudates extravasated into the intima of coronary arteries and aorta.

In terms of general pathology, this process represents the genesis of atheromata from either inflammatory lesions or thrombotic lesions, or a combination of these.

4:15

17. Histochemical and Electron Microscopic Studies on Cholesterol Absorption by Human Atheromatous Plaques

Abel A. Lazzarini. From the New York University School of Medicine, New York 16, New York

The absorption and deposition of aqueous micro-emulsions of C^{14}-labelled cholesterol, steroids and fatty acids in the intima of the aorta and coronary vessels of patients with severe atherosclerosis were followed in short-term organ cultures by autoradiography and electron microscopy.

Two different cell types could be distinguished by their lipid uptake and the relation of subcellular structures to cytoplasmatic droplets.

The absorption of cholesterol and saturated fatty acids by intimal cells of atherosclerotic lesions was 56 to 78 per cent higher than in control specimens. It was found to occur simultaneously with a reduction in oxidative cell processes and an increase in mucopolysaccharide production.

Changes in cell membrane permeability and competitive pinocytosis by ferritin and other colloids were able to modify lipid deposition.

4:30

18. A Study of Human Coronary Profiles

O. J. Pollak and Patsy S. Morrow. From the Dover Medical Research Center, Inc., Dover, Del.

A method for the study of the transverse profiles of coronary arteries has been developed. The technic is based on preparation of plaster casts of longitudinally opened arteries, segmentation of the casts, tracing of the contours of the segments, enlarging of the tracings to make possible exact measurements. The number, degree and localizations of elevations which encroach upon the vascular lumen and the unevenness of the surface are recorded.

Comparison was made of coronary artery profiles (1) from patients who died of first myocardial infarction, (2) from patients who died of second myocardial infarction (3) from patients with post-infarction myocardial scars but dead of other causes, and (4) from subjects with intact myocardium.

This study led to determination of the limit of minimum arterial width and maximum thickening of the wall which, combined, resulted in anoxic anatomical myocardial damage. Prorating the minimum width to maximum thickness and expressing the latter as "1", a ratio of 2 or less (1.9, 1.8, etc.) appeared critical, regardless whether the intimal surface was even or distorted by one or

more prominences. The location of stenosis from the arterial orifice determined the size of the affected myocardial segment.

Extension of the study may lead to a similar index which could be applied to functional myocardial alterations. The method lends itself to correlation of arterial disease with such clinical data as age, sex, body surface, blood pressure, electrocardiograms, etc.

4:30-4:45 Intermission

4:15

19. Damages of "Silicone-like Property" of Vascular Endothelium by Arteriosclerogenic Substances and Their Prevention by Nialamide

Takio Shimamoto. From the Department of Clinical Physiology and Medicine, Tokyo Medical and Dental University, Tokyo, Japan

The endothelial surface of blood vessels possesses a special characteristic like silicone. It prevents the adherence of blood platelets and leukocytes and preserves the fluidity of the blood.

Recently the author found that several amines, polypeptides, lipids and high molecular weight substances induce swelling of endothelial cells resulting in the damaging of their "silicone-like property." The swollen endothelial cells exhibit stickiness to platelets and leukocytes and form white thrombi. At the same time the platelet count decreases and the blood clotting time shortens. It was also found that repetitious administration of these substances to various species of animals induces intimal arteriosclerosis. A large difference in the threshold dose according to the kind of substances and species of animals was found.

If there should exist a protective measure for preserving the "silicone-like property" against arteriosclerogenic substances, such a measure might be valuable in the fight against the problem of arteriosclerosis and their thromboembolic complications.

Using direct observation according to Sandison-Clark, the author found that nialamide (10-100 mg. orally) prevents the damaging effect of three arteriosclerogenic substances, i.e., adrenaline (0.1-50 γ/Kg., i.v.), cholesterol (1-3 gm./Kg. orally) and bacterial polysaccharide (0.1-1 mg./Kg., i.v.), on the silicone-like property of the blood vessels in all 21 rabbits, and these findings were filmed.

The immediate effect of decreasing the platelet count and shortening the blood clotting time of arteriosclerogenic substances (0.1 g. of adrenaline intravenously, 90 cc. of fresh cream plus 5 gm. of butter orally in all 22 men and 0.1-1 g./Kg. of adrenaline or 1 mg./Kg. of bacterial polysaccharide intravenously or 1-3 gm./Kg. of cholesterol orally in all 30 rabbits) were also found to be prevented by oral pretreatment with nialamide of 10 mg. in rabbit and of 75-100 mg. in man.

5:00

20. The Effects of Serum Sickness on Cholesterol Atherosclerosis in the Rabbit

James C. Roberts, Jr. From the East Tennessee Baptist Hospital, Knoxville, Tenn.

Many recent studies indicate differences between the severity of human coronary atherosclerosis and aortic atherosclerosis. These experiments were designed to observe any differences in coronary and aortic atherosclerosis between rabbits on high cholesterol diets, with and without injections of a soluble foreign protein, bovine serum albumin (BSA). BSA regularly produces serum sickness arteritis in over 95 per cent of rabbits injected as in these experiments. The first experiment was terminated by sacrifice after 3 months on high cholesterol diet. The second experiment included the addition of a 3-month low cholesterol diet "recovery period" after the initial 3 months on test.

Results of the first experiment include a) An increase in occlusive coronary artery atheroma in the BSA—Cholesterol group when compared to the Cholesterol only group; b) Similar aortic atheromata in both group and; c) Elastic tissue alterations similar in all 4 groups.

Results of the second experiment include a) An increase in occlusive coronary artery atheroma and myocardial infarcts in the BSA—Cholesterol group when compared to the Cholesterol only group; b) Aortic atheromata similar in area covered but differing qualitatively between the groups, and c) Elastic tissue alterations similar in all 4 groups.

The above observations will be discussed in reference to localization of atherosclerosis, serum sickness and elastic tissue changes.

5:15

21. Influence of Type of Dietary Fat upon the Ability of Cholesterol to Enter the Artery Wall

Seymour Dayton and Sam Hashimoto from the Veterans Administration Center, Los Angeles 25, California

There has been some speculation in recent years that various cholesterol esters might differ in their

proneness to become deposited in artery walls. However, experimental evidence in support of this concept has not been reported.

In the present study, young adult female rats were fed diets containing 30 per cent (by weight) of either coconut oil (iodine value 10) or safflower oil (iodine value 125). After 14 days on such a diet, each animal received a single dose of cholesterol-4-C^{14} by stomach tube, and continued thereafter on the same ration. Animals were sacrificed, in groups of 5 to 8, at intervals from 1 day to 42 days after receiving the labeled cholesterol.

The interrelationships of the time curves of specific activity of cholesterol isolated from plasma and from aorta indicate that most of the aorta cholesterol was derived from plasma cholesterol, on either diet. The specific activity of aorta wall cholesterol rose faster in the coconut oil group than in the animals on safflower oil, and peak specific activity was higher on the coconut oil diet. Differences in plasma cholesterol specific activity were small and inconstant, and could not have accounted for the differences in the aorta cholesterol specific activity curves. Furthermore, plasma cholesterol concentrations were comparable on both diets. It is tentatively proposed, pending additional data, that coconut oil feeding rendered the plasma cholesterol and/or cholesterol esters more capable of entering the aortic wall than was the case in the safflower oil group.

THURSDAY MORNING
OCTOBER 20, 1960

CRYSTAL ROOM
Sheraton Jefferson Hotel

Liese Abell, Presiding

9:00

22. Effects of Long-Term Estrogen Therapy on Serum Cholesterol - Lipid - Lipoprotein Levels and on Mortality in Middle-Aged Men with Previous Myocardial Infarction

Jeremiah Stamler, Louis N. Katz, Ruth Pick, Lena A. Lewis, Irvine H. Page, Alfred Pick, Benjamin M. Kaplan, David M. Berkson and Dolores F. Century. From the Heart Disease Control Program, Chicago Board of Health; Cardiovascular Department, Medical Research Institute, Michael Reese Hospital and Medical Center, Chicago, Illinois; and the Research Division, Cleveland Clinic Foundation, Cleveland, Ohio

A long-term study was completed evaluating estrogen therapy in 275 men under age 50 surviving previous myocardial infarction. Placebo and estrogen-treated groups were divided into subgroups, Series and Off-Series, good and poor risk. The Off-Series group was made up chiefly of men with 2 or more previous myocardial infarctions, i.e., men with a poor long-term prognosis. Hormone was given orally as mixed conjugated equine estrogens (final dosage: 10 mgm. daily), producing feminizing effects in all men without toxic effects. Estrogens induced sustained alterations in serum cholesterol-lipids-lipoproteins. Mortality was analyzed by statistical calculation of survival at 3-month intervals, with and without exclusion of events (loss, mortality) in the first 2 and 6 months of the study. Otherwise, all patients were included in these survival analyses irrespective of lapses from therapy and drop-out. Lost cases were traced to December 31, 1959. For good risk and Series patients, mortality rates were similar in the estrogen-treated and placebo groups. For poor risk and Off-Series patients, mortality rates in the placebo groups were 2- to 4-fold higher. Further subgroups not started on estrogens until at least 3 to 6 months after myocardial infarction had a 2- to 6-fold lower mortality than their matched placebo controls. The data indicate that estrogens may be efficacious in the long-term treatment of coronary disease, particularly for high-risk patients, when treatment is not begun until 3 to 6 months after the previous myocardial infarction, low initial dosage is utilized, and higher dosage gradually instituted.

9:15

23. Further Studies of the Hypocholesteremic Effect of Methyltestosterone

Erwin H. Mosbach and Liese L. Abell. From Columbia University Research Service, Goldwater Memorial Hospital and Departments of Biochemistry and Medicine, College of Physicians and Surgeons, Columbia University

The observation by Furman that the oral administration of 17 α-methyltestosterone causes a profound reduction of the serum cholesterol concentration of dogs fed low-cholesterol diets has been confirmed. This effect was observed on a diet consisting of commercial dog chow; on this same diet supplemented with either corn oil or lard; and on this diet supplemented with horsemeat and either corn oil or lard. The cholesterol content of both the alpha- and beta-lipoprotein fractions of the serum was reduced in each case.

Addition of 1.5 to 3 per cent cholesterol to each of the test diets produced increases in the serum cholesterol levels. Administration of methyltestosterone significantly reduced the serum cholesterol levels in these dogs fed either the cholesterol-containing low fat diet or this diet supplemented with corn oil. However, in dogs fed cholesterol-containing diets supplemented with both horsemeat and either corn oil or lard, methyltestosterone failed to lower total serum cholesterol concentrations. Although there was a profound fall in the cholesterol content of the alpha-lipoprotein fraction in every case, this was accompanied by an increase of the beta-lipoprotein fraction, so that in many of the dogs the total cholesterol concentration increased. Experiments are now in progress on the effect of methyltestosterone upon the lipoprotein levels of dogs maintained on low fat diets supplemented with horsemeat and cholesterol.

9:30

24. Urinary Ketosteroid Excretion and Serum Lipid Changes During Oral and Intramuscular Androsterone Administration

William D. Cohen, Norio Higano and Roger W. Robinson. From The Memorial Hospital, The Research Laboratory, Worcester 5, Massachusetts

Androsterone was administered orally at approximately 100 mg. daily for 1 month to 13 male subjects with coronary heart disease, and intramuscularly at 50 mg. daily (in a benzyl alcohol-sesame oil vehicle) for a similar period to 4 men. An additional subject tolerated intramuscular administration for only 1 week because of severe local reactions. In agreement with the recent report by Hellman, et al., a hypocholesterolemic effect was seen within 1 week of intramuscular androsterone administration in 4 of the 5 subjects. A comparable decrease in the cholesterol content of the β-lipoproteins was also found, with no change in α-lipoprotein cholesterol. In contrast, oral administration of androsterone had little effect on the serum lipids. The recovery of 39 per cent (36 mg. when 92 mg. were given orally) of the administered dose in the urine, of which 33.8 mg., or 93 per cent was released by β-glucuronidase hydrolysis, indicated that there was adequate gastrointestinal absorption of androsterone. A larger proportion of the intramuscular androsterone, 31.3 mg. or 62 per cent of the 50 mg. dose in 1 subject and 34.4 mg. (68 per cent) in a second, was recovered in the urine. The impracticality of intramuscular and the ineffectiveness of oral administration of androsterone militates against its adoption as a hypocholesterolemic agent for clinical use.

9:45

25. Androsterone Influence on Serum Lipids and Lipoproteins: Androgenic or "Thyromimetic"?

Robert H. Furman and R. Palmer Howard. From the Oklahoma Medical Research Institute, Oklahoma City 4, Okla.

Androsterone production is diminished in hypothyroidism and increased by thyroid administration to hypothyroid or euthyroid subjects. Androsterone administration caused a variable hypocholesterolemic response (0-40 per cent) in myxedematous, hypercholesterolemic and normocholesterolemic subjects. On the basis of these studies Hellman, Gallagher, et. al. (*J. Clin. Endo. and Metab. 19: 936, 1959*) postulated that the hypocholesterolemic effect of thyroid was mediated in part by androsterone which they labelled "thyromimetic."

Androsterone is a weak androgen and as such could be expected to cause changes in serum lipoproteins characteristic of androgen: decreased α-lipoprotein and α/β ratio, unchanged or decreased β-lipoprotein, unchanged or decreased serum cholesterol. Thyroid on the other hand, causes decreased β-lipoprotein, increased α/β ratio, unchanged or increased α-lipoprotein, and decreased cholesterol.

Metabolic and serum lipoprotein effects of triiodothyronine (up to 300 micrograms daily) and androsterone (up to 160 mg. daily) were compared in two myxedematous, one hypercholesterolemic and one normocholesterolemic subject under metabolic balance conditions.

In respect to effects on α- and β-lipoproteins, androsterone was androgenic and not "thyromimetic." A slight anabolic effect was noted. Triiodothyronine produced α- and β-lipoprotein changes characteristic of thyroid, as well as nitrogen loss.

An expected finding of great interest was the reduction in low density lipoproteins ($d > 1.006 < 1.019$ and $d < 1.006$ g./ml.) noted in the 2 subjects in whom they were elevated initially. This reduction in low density lipoproteins was responsible for the hypocholesterolemic effect of androsterone which was noted only in these 2 subjects. This may explain the variability of response noted by Hellman, et. al. Triiodothyronine also caused similar low density lipoprotein changes.

Thus it would appear that while androsterone is "androgenic" in respect to α- and β-lipoproteins (and therefore not "thyromimetic") it shares with thyroid the property of reducing serum levels of low density lipoproteins. This is a previously unrecognized effect of androsterone and is under further study.

10:00

26. Dietary Lipids and Blood Hydrocortisone

Daniel A. Sherber and Martin Marcus. From the Metabolic Research Laboratory, Fordham Hospital, New York, N. Y.

In an attempt to correlate data which implicates the endocrine system as well as dietary lipids in the pathogenesis of atherosclerosis, studies were done to determine whether a high-fat meal constituted "stress" for the human as determined by the level of blood hydrocortisone.

The results indicate that high fat ingestion is associated with a profound decrease in circulating hydrocortisone evident within 1 to 3 hours after eating. The hydrocortisone trough did not correspond to the peak of lipemia. Hydrocortisone values frequently diminished to zero. Hydrocortisone was determined by the Peterson method and Nelson-Samuels technique. Selected samples were also separated in a Zaffaroni chromatography system and its absence was substantiated by zero values with the Peterson method.

Isocalorically substituted minced meals of 1000 calories depressed hydrocortisone values somewhat from the early morning peak but never equal to the depression induced by a high-fat diet. Continuous fasting with blood samples drawn during a 4-hour period showed blood hydrocortisone to remain nearly constant.

10:15

27. Cortisone Effect in Rabbits on Metabolic Behavior of a Single Cholesterol Meal

Abraham Dury. From the Research in Aging Section, General Medical Research, Veterans Administration Hospital, Pittsburgh 40, Pa.

Cortisone administration minimizes atheromatous development in hypercholesterolemic rabbits. Its mechanism is not known but one possible mode of cortisone action is upon dietary cholesterol metabolism. Observations are reported on behavior of a single meal containing 1 gm. of cholesterol-4-C^{14} (10 μc.) from 3 hours to 7 days after feeding to untreated and cortisone injected (5 mg./rabbit/day for 2 weeks) normal fed rabbits. Chemical and C^{14}-free and esterified cholesterol were determined in ileum, liver, plasma and aorta. In cortisone-treated rabbits, a larger part of labeled cholesterol meal was incorporated in the free and the ester cholesterol of the ileum, liver and plasma with maxima specific activities 2-3 times that of controls. In both types of animals maxima specific activities were reached at the same time for ileum free and ester cholesterol (6 hours) and the free cholesterol of plasma and liver (48 hours) after cholesterol-4-C^{14} meal. By contrast, liver and plasma ester cholesterol reached maximal specific activities after labeled cholesterol meal in cortisone-treated rabbits but in neither type of rabbit was maximum specific activity reached 7 days after the labeled test meal. Also, only in the cortisone-treated rabbits was dietary cholesterol incorporated and turned over in the ester cholesterol of the aorta and dietary cholesterol present as liver ester cholesterol behave differently from the controls. It is concluded that cortisone caused increased absorption and greater turnover rates of dietary cholesterol in all examined tissues and particularly modified the metabolic handling of dietary cholesterol present as ester cholesterol in the plasma, liver and aorta.

10:30-10:45 Intermission

10:45

28. Relationship Between Tissue Distribution of Thyroxin Analogs and their Effects on Cholesterol Metabolism

Charles H. Duncan and Maurice M. Best. From the Department of Medicine, University of Louisville School of Medicine, Louisville 2, Ky.

D-triiodothyronine (D-T3), tetraiodothyroformic acid (TFA-4) and tetraiodothyropropionic acid (tetraprop) labelled in the 3′ 5′ positions with I^{131} were injected intravenously into male rats (.0016 to .004 μM of hormone labelled with 10 to 20 μc I^{131} per 250 Gm. rat), groups of animals killed at 40 minutes and 2, 6, 18 and 54 hours later and the concentration of radioactivity in plasma, liver, kidney, heart, muscle and brain measured. Of the 3 compounds, D-T3 had the shortest biologic half-life, TFA-4 the longest and tetraprop an intermediate rate of excretion. Significant differences in distribution of the I^{131} label were present at 40 minutes and persisted throughout the 54 hour period of study. The ratios, concentration in tissue/initial concentration in total body at 40 minutes for D-T3, TFA-4 and tetraprop were: serum, .46, 13.80, 7.52; Liver, 11.42, 2.96, 2.39; kidney, 19.14, 2.05, 1.70; heart, .32, 1.68, 1.12; muscle, .12, .23, .21; and brain, .02, .19, .13, respectively. The disproportionate effect of D-T3 on liver cholesterol (Best and Duncan, 1959) may thus be due to its relatively greater concentration in liver than in peripheral tissues. However, the similarly exaggerated effect of TFA-4 on cholesterol metabolism is not explicable on this basis, since its distribution did not differ significantly from that of tetraprop, which displays no such dissociation of effects.

11:00

29. Coronary Atherosclerosis in Rats Exposed to Cold

Edward A. Sellers and Donald G. Baker. From the Department of Pharmacology and Banting and Best Department of Medical Research, University of Toronto, Toronto, Ontario, Canada

Rats (originally Wistar) fed a commercial laboratory ration developed a mild degree of coronary lipoidosis after long periods. The incidence and severity of the lesions were increased greatly by continuous exposure to cold, (2° C.).

In the cold, hyaline material containing blood elements and lipid occurred subintimally in amounts which sometimes occluded the lumen. A high fat diet containing 2 per cent cholesterol fed to old rats (approximately 2 years) especially those which had lived in a cold environment produced severe atherosclerotic lesions within 6 weeks. Interstitial necrosis and a few infarcts were observed. The same diet fed to rats for 76 weeks continuously produced fewer lesions, suggesting the possibility of adaptation to the particular diet.

The pathogenesis of some of the more severe coronary lesions was explained by the presence of miniature dissecting aneurysms, some involving plasma only and some whole blood. Photomicrographs illustrate these findings.

11:15

30. Cholesterol Synthesis in Normal and Abnormal Human Subjects

Laurance W. Kinsell, George D. Michaels, Geoffrey Walker and Joyce Conklin. From the Institute for Metabolic Research, Highland-Alameda County Hospital, Oakland, Calif.

The present study was undertaken to determine whether the mechanism of the hypocholesterolemic effect of a variety of natural and synthetic fats, including safflower oil, "unsaturated margarines," ethyl linoleate, and certain purified fish oils was attributable to decreased rates of formation or increased rates of removal of plasma cholesterol. Tracer doses of C^{14}-labeled mevalonic acid were administered intravenously and the rate of incorporation of the C^{14} in plasma cholesterol determined over standard periods of time. In some of the subjects, rate of disappearance of intravenously administered, biologically labeled plasma cholesterol from the plasma was also determined under identical dietary conditions.

The studies indicate that unsaturated fats produce a major portion of their effects upon plasma lipids by decreasing the rate of cholesterol synthesis. The amplitude of effect varied from patient to patient, particularly in those individuals with essential hypercholesterolemia, and in some of the atherosclerotic individuals.

The possible clinical and physiologic significance of these observations will be discussed.

11:30

31. The Fatty Acid Patterns of Serum Chylomicrons of Patients with Essential Hyperlipemia Before and After Cream, Corn Oil or Coconut Oil Feeding

Peter T. Kuo, Arthur F. Whereat and Ezra Staple. From the Hospital and School of Medicine, University of Pennsylvania, Philadelphia 4, Pa.

The effect of dietary fat upon the fatty acid pattern of serum chylomicrons of 7 hyperlipemics and 5 normal controls was studied. Serum chylomicrons were isolated by flotation into the supernatant saline (sp. gr. 1.005) at 58,000 × g. for 30 minutes. The creamy and subnatant saline layers were removed separately and the fatty acid compositions of each layer was determined by gas chromatography. The fatty acid patterns of the creamy and saline layers of fasting hyperlipemics were practically identical; and they were similar from one patient to another. Hyperlipemics had increased palmitoleic and decreased stearic and linoleic fractions compared to non-lipemic controls. Following prolonged fat restriction, the linoleic peak in the serum fat pattern of 3 hyperlipemics was increased. The compositions of serum chylomicrons and depot fat were similar in untreated patients. However, in non-lipemics and in fat-restricted lipemics, the compositions of the blood and tissue triglycerides were different. The fatty acid compositions of the serum chylomicrons, obtained after cream, corn oil or coconut oil feeding changed progressively to become practically identical with that of dietary fat after 3-4 hours in normals and in 9-12 hours in hyperlipemics. The subnatant saline layer of all post-prandial specimens contained very little of the ingested fat. The study indicates that dietary fat contributes directly to alimentary lipemia in health and disease. The progressive incorporation of dietary fat into serum chylomicrons, while their concentrations were rising over 12 hours after meals, suggests intensified fat absorption can be a factor in the production of hyperlipemia.

11:45

32. The Effect of Corn Oil and Hydrogenated Coconut Oil on the Liver Cholesterol Content in Human Subjects

James B. Carey, Jr., and Ivan D. Frantz, Jr. From the Cardiovascular Research Laboratory, Department of Medicine, Medical School, University of Minnesota, Minneapolis, Minn.

In experimental animals the feeding of corn oil has resulted in increases in the cholesterol content of the liver. In order to determine if such a regimen causes an increase in cholesterol in the human liver, 12 apparently healthy male volunteers with high normal concentrations of serum cholesterol were assigned alternately to 2 groups of 6 men each. A punch biopsy of the liver was obtained from each subject. For the following month 3 ounces of corn oil and 3 ounces of hydrogenated coconut oil were added to the diets of Groups I and II, respectively. A second liver biopsy was then obtained from each man. The serum cholesterol fell an average of 22 mg. per cent in Group I ($p < 0.01$) and rose an average of 11 mg. per cent in Group II (not statistically significant). Liver cholesterol concentrations were measured by a micro modification of the Abell method, and expressed in milligrams per 100 grams of wet liver by comparison with the total protein. In Group I, cholesterol fell by an average of 159 mg./100 gm. (25 per cent of the initial values, $p < 0.05$). In Group II there was an average rise of 10 mg./100 gm., (not statistically significant).

It is concluded that in man, transfer of cholesterol to the liver is not involved in the lowering of serum cholesterol produced by feeding 3 ounces of corn oil daily.

THURSDAY AFTERNOON

Crystal Room

12:00-2:15 Luncheon
G. Lyman Duff Memorial Lecture, Howard B. Sprague: "Emotional Factors in Coronary Heart Disease"

Jeremiah Stamler, Presiding

2:30

33. The Effect of Nicotinic Acid on Essential Hyperlipemia

Kurt Hirschhorn, Winnifred Seegers and Burton S. Sklarin. From the New York University Medical Center, New York 16, New York

Nicotinic acid has been shown by several investigators to lower serum cholesterol in primary and secondary hypercholesterolemias. We have studied several patients with essential hyperlipemia for varying periods of time, up to 9 months. Each of these patients had had long periods of therapeutic trial with dietary regimens as well as long baseline control periods.

Serum cholesterol fell in these patients on nicotinic acid administration to a degree comparable to the fall in simultaneously treated hypercholesterolemics. Serum triglyceride and optical density fell sharply in the hyperlipemics. Xanthomatosis, when present, appeared to diminish. When nicotinic acid was stopped, triglyceride and cholesterol promptly rose.

Among the patients treated with nicotinic acid were members of a hitherto unreported family of essential hyperlipemics; which included several homozygous children with hepatosplenomegaly and xanthomatosis. Genetic data on this family will be presented.

2:45

34. Nicotinic Acid, Food Intake and Serum Cholesterol

Rudolph Altschul and Terry A. Smart. From the Laboratory of Gerontology, Department of Anatomy, University of Saskatchewan, Saskatoon, Canada

Nicotinic acid (n.a.) in large doses decreases serum cholesterol in man and several species. Whether the improvement of angina pectoris following such treatment, as already reported in 6 publications, is coincidental, psychogenic or specifically connected, requires further investigation. The effect of n.a. on cholesterol has been ascribed to increased oxidation (Altschul; Perry; Kritchevsky, et. al.); to interference with activity of coenzyme A (Schon; Schade and Saltman); to stimulation of the r.-e. system (Kraupp, et. al.); and to anorexia (Friedman and Byers; Duncan and Best). If this last explanation was true, one may expect that decrease in food intake would lower serum cholesterol. This seems to be the case if the decrease is maintained over prolonged periods (Walker, et. al., 1953) but even then the lowering of serum cholesterol is much less than that by n.a. However since n.a. lowers serum cholesterol already within ½ - 24 hours (Altschul in rabbits and prairie gophers; Kraupp, et. al. and Comesano, et. al., in dogs; Altschul, et. al., Guarini and Martinez, in humans) anorexia cannot be responsible. As a matter of fact, Hueper (1949) warned against excessive starvation hypercholesterolemia through the mobilization of depot fat. Even a less drastic loss of weight in humans (3.6 lbs. per week) is followed by a slight increase of serum cholesterol after the first 15 days (Walker, et. al.). To put this problem to a stern test we decreased for 18 rabbits the food intake for 2 days to 1/3 of calorie value and for 25 rabbits withdrew all food for the same period. In both groups the serum cholesterol increase was highly significant (+19.8 per cent and 19.85 per cent), with a loss in body weight of 3.1 per cent and 3.2 per cent, respectively.

3:00

35. Studies During Reduction of Serum Cholesterol Levels in Humans by Nicotinic Acid: Enzymatic Reactions (Sulfbromphthalein, Transaminase, Alkaline Phosphatase), Nicotinic Acid Blood Levels, and C^{14}-Acetate Incorporation

William B. Parsons, Jr. From the Jackson Clinic and Jackson Foundation, Madison, Wisconsin

Four years of experience with large doses of nicotinic acid (3 to 6 Gm. daily) in hypercholesteremic patients continues to confirm previously reported results: prompt and sustained reduction of serum cholesterol levels in most patients without dietary restriction. Indirect evidence points to enzymatic alterations in the liver (and elsewhere) as one mechanism of action. Marked abnormalities in function tests involving enzymes (sulfbromphthalein, transaminase, alkaline phosphatase) are rapidly reversible by discontinuing therapy and have not been consistently associated with histologic evidence of hepatic damage. Delayed-release nicotinic acid preparations have resulted in greater incidence of abnormality in the enzymatic tests, more nausea and vomiting, and possibly greater, more rapid reduction in serum cholesterol levels than the same doses of plain nicotinic acid. Further study of the significance of these observations are in progress, determining serum levels of nicotinic acid and nicotinuric acid by bioassay, but results are inconclusive at the time of submission of this abstract.

The incorporation of C^{14}-acetate into plasma cholesterol (free and esterified) and erythrocyte cholesterol during administration of nicotinic acid and nicotinamide is being studied by the Gould technic (since the amide does not reduce serum lipids). Preliminary results show curves during nicotinic acid administration (3 patients) similar to those reported by Gould and associates for normal individuals. Results on incorporation during nicotinamide administration are as yet incomplete.

3:15

36. Further Studies of Effects of MER-29 in Man

Daniel Steinberg, Joel Avigan and Eugene B. Fingelson. From the National Heart Institute, National Institutes of Health, Bethesda, Maryland

Following the report by Blohm and co-workers that MER-29 strongly inhibited cholesterol biosynthesis, Avigan and co-workers demonstrated that the drug caused an accumulation of 24-dehydrocholesterol (I) in the rat and an inhibition of the conversion of I to cholesterol (II). The present studies in humans show that MER-29 (100 to 250 mg./day) causes an accumulation of I in the serum which reaches fairly stable levels of 20 to 40 per cent of the total circulating sterols after 2 to 3 weeks of treatment. Levels of I were estimated using a method based on the different color yields with I and II at two wave lengths in the Liebermann-Burchard reaction. Since I gives a lower color yield than II, apparent "cholesterol" levels in much of the data reported in the literature on MER-29 are lower than the true total sterol levels (I + II). The free: total 24-dehydrocholesterol ratio was not significantly different from the free: total cholesterol ratio.

When mevalonic acid-2-C^{14} was injected intravenously into patients on MER-29, the specific radioactivity of serum I was much higher (15 to 50 x) than that of II and remained so from 1 to 24 hours after injection.

It is concluded that also in man the primary site of action of MER-29 is the inhibition of conversion of I to II. Using each patient as his own control, the peak *total* sterol radioactivity after injection of mevalonic acid-2-C^{14} was compared on and off MER-29. As much as a 50 per cent inhibition on MER-29 was observed in some patients. The rate of esterification of I and II appear to be similar.

3:30

37. Effect of SKF 7732 and SKF 7997 on Cholesterol Biosynthesis *In Vitro*

William L. Holmes and Joan D. Bentz. From the Research and Development Division, Smith, Kline & French Laboratories, Philadelphia, Pennsylvania

Greenberg and Herndon have shown that SKF 7732 [tris(2-dimethylaminoethyl) phosphate] and SKF 7997 [tris(2-diethylaminoethyl) phosphate] effectively lower the serum cholesterol level of naturally hypercholesterolemic dogs. Preliminary experiments *in vitro* showed that SKF 7732 inhibited the conversion, by rat liver homogenates, of acetate-C^{14} to digitonide precipitable sterol. When compared with the control, however, this compound had no effect on the incorporation of acetate-C^{14} into the total non-saponifiable lipid. Subsequent studies showed that SKF 7732 and its ethyl analog, SKF 7997, both inhibit the incorporation, *in vitro*, of mevalonic acid-2-C^{14} into digitonide precipitable material, but not into the total nonsaponifiable fraction. Chromatographic studies of the nonsaponifiable lipids on Al_2O_3 revealed the presence of 3 radioactive components.

One of these, the digitonide precipitable fraction, was present in only small amount in the material from the inhibited reaction mixture. The other 2, less polar fractions, were found to accumulate in the inhibited reaction mixtures. Studies on the nature of the accumulated intermediates show that this class of compounds inhibits one or more reactions lying between mevalonic acid and lanosterol on the biosynthetic pathway leading to cholesterol.

3:45-4:00 Intermission

4:00

38. Serum Lipoprotein Alterations Induced by an Orally Active Heparinoid, Sulfopolyglucin

Ernest Q. King, Martin A. Seidell and Adolph Surtshin. From Sepulveda, California

Oral administration to man and animals of sulfopolyglucin (SPG), a characterized sulfated polysaccharide, is followed by appearance of a lipoprotein lipase in blood plasma. Gastrointestinal absorption is enhanced by concomitant ingestion of sodium 'Versenate' (V). A mixture of SPG and V (4:1) was given to 28 human subjects in daily doses of 2-6 Gm. (of SPG) for periods of 1 to 6½ weeks. Sf° 12-400 serum lipoprotein concentrations, studied in 26 subjects, decreased impressively in 15, in many of whom pretreatment values had been relatively high. Dramatic lowering was observed in 4 of 6 subjects given single doses of 2 Gm. daily: pretreatment values—293, 211, 129, 112 mg. per cent; after 2 weeks of treatment—136, 156, 94, ?; after 4 weeks of treatment—39, 39, 53, 36 mg. per cent, respectively. The daily 2 Gm. dose was still being well tolerated by all 6 subjects after 6 weeks of treatment. In other subjects, serum lipoprotein concentrations, depressed in the course of 6 weeks of treatment with daily doses up to 6 Gm., were still below pretreatment values on the fiftieth day after discontinuance of treatment. Lee-White whole blood coagulation times were not affected.

4:15

39. Phospholipid Synthesis in Atherosclerosis Susceptible and Resistant Pigeons

H. B. Lofland, T. B. Clarkson and C. Artom. From the Bowman Gray School of Medicine, Winston-Salem, North Carolina

Certain reports indicate that differences in susceptibility to atherosclerosis may be related to the ability of various animal species to synthesize phospholipids. It has also been suggested that the bulk of arterial phospholipid arises by synthesis *in situ*, rather than by deposition from plasma, especially in cholesterol-fed animals. Our observation that certain breeds of pigeons develop spontaneous atherosclerosis, while other breeds are resistant to this disease, suggested we investigate phospholipid synthesis in these animals.

White Carneau (susceptible) and Show Racer (resistant) pigeons were injected with P^{32}. After 6 hours (which time interval falls within the ascending portion of time-specific activity curves), the birds were sacrificed and the specific activities of lipid and inorganic P in liver, plasma, and aorta were determined. In non-cholesterol fed birds of both breeds, the specific activity of lipid P was lower in the aorta than in plasma. The difference in specific activity between plasma and aorta phospholipids seemed to progressively decrease when cholesterol was fed. In no case were differences between the 2 breeds demonstrable.

In other experiments still in progress, liver slices were incubated with methionine-C^{14}-methyl, and the amounts of isotope incorporated into phospholipids were determined. Preliminary data suggest that when the values are referred to the whole organ, livers of Show Racers incorporate more isotope than do livers of White Carneaux.

4:30

40. Characteristics of Cobalt-Induced Lipemia in Rabbits

Laszlo L. Fekete, Walter F. Lever and Edmund Klein. From the Harvard School of Medicine and Tufts University School of Medicine, Boston, Massachusetts

Oral, intravenous, intracisternal, and intracerebral administration of cobaltous chloride produced hyperlipemia in rabbits. The average doses required were: 100 mg. for oral, 50 mg. for intravenous, 1.0 mg. for intracisternal, and 0.5 mg. for intracerebral administration. Maximal lipemia response was observed in young animals (1600 Gm.) of both sexes of the New Zealand strain and during the summer. Cobalt, if administered in conjunction with isomolecular quantities of EDTA, or large amounts of methionine, did not produce hyperlipemia.

Cobalt-induced hyperlipemia and human idiopathic hyperlipemia were similar in regard to: 1) relative elevation of the 3 lipid fractions, cholesterol, phospholipid and neutral fat; 2) electrophoretic and ultracentrifugal pattern of serum lipoproteins, and 3) response to administration of heparin. Cobalt-lipemic sera inhibited lipoprotein

lipase activity when measured turbidimetrically but did not inhibit release of unesterified fatty acids, predominantly from β-lipoproteins.

Cobalt-induced lipemia was diminished or prevented by large doses of cortisone, thyroxin, estradiol (regardless of sex), and insulin. Testosterone increased the lipemia. Glucagon and thymus extracts had no effect.

Histologic examinations failed to reveal lesions specifically related to the development and degree of lipemia.

Lipemia could be induced by lower doses of cobalt and appeared earlier following intracisternal and particularly localized intravertebral (hypothalamical) injection. This may indicate that the development of hyperlipemia is initiated by the action of cobalt ions on the central nervous system.

4:45

41. In Vitro Effects of Triton WR-1339 on Dog Plasma Lipoproteins and Chylomicra

Angelo Scanu and Pasquale Oriente. From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio

Triton (a non-ionic detergent) was added *in vitro* to fasting dog sera and to separated β- and α-lipoproteins labeled in the protein moiety were used. Dose, temperature, pH and time of incubation were studied. Following incubation and prolonged dialysis the mixtures were separated by preparative and analytical ultracentrifuge, paper and starch electrophoresis. The chemical composition of the fractions was then determined. When labeled material was used, determination of radioactivity completed the analyses. Optimal conditions for Triton activity were: 37° C, pH 7.2, and 2 hours of incubation. α-Lipoproteins exhibited marked changes proportional to the amount of Triton added. Triton formed a complex with the lipid moiety; by increasing the amount of detergent, lipids were progressively pulled from the lipoprotein up to a point (Triton-lipoprotein ratio 20:1) at which practically all protein was freed of lipids. This phenomenon was particularly evident in starch patterns. This lipid-free protein was able to recombine with lipids. β-Lipoproteins were also freed of most of the lipid moiety by Triton. Higher doses of detergent (Triton, lipoprotein 40-80:1) were, however, necessary. Chylomicra, labeled in their α-lipoprotein moiety with I^{131}, were freed of this protein by incubation with Triton. Addition of Triton to chylomicra prevented their interaction with the lipid-free protein moiety of α-lipoprotein (Fed. Proc. 19: 230, 1960).

5:00

42. Some Histochemical Observations on the Aorta of Rats Fed an Essential Fatty Acid Free Diet

Maurice Sandler and Geoffrey H. Bourne. From the Department of Anatomy, Emory University, Atlanta, Georgia

In previous work we have reported on the distribution of enzymes dephosphorylating adenosine monophosphate and adenosine triphosphate in animals and in human aortas. In the human aortas we found a decrease in adenosine triphosphatase in atheromatous areas and in a number of seemingly normal isolated areas. The present report involves a study on 30 female rats (discarded breeders, Holtzman Strain) fed from 2 to 6 weeks on a synthetic diet free of essential fatty acids. Food was removed from the animals 4 hours prior to sacrifice by decapitation. A decrease in the adenosine triphosphatase activity was seen beginning at the fourth week and by the sixth week all animals on the diet showed a decrease in the activity of this enzyme in the aorta. There was no observable change in the histochemical enzymic dephosphorylation of adenosine monophosphate, creatine phosphate, diphosphopyridine nucleotide, triphosphopyridine nucleotide, pyridoxal phosphate or β-glycerophosphate. The experimental decrease in adenosine triphosphatase activity shown above was not accompanied initially by any histological change in the aortic wall. This fact together with the decrease of ATPase in a histologically differentiated atheroma and in spots in the normal parts of the same human aorta suggests that the change in enzyme activity precedes histological change and may be a primary factor in initiating the morphological lesion.

5:15

43. The Influence of Dietary Fats on the Fatty Acids of Atheromatous Plaques and Various Tissues in Rabbits

Naip Tuna, Mary J. Sundeen and Mary L. Louden. From the Cardiovascular Research Laboratory, Department of Medicine, Medical School, University of Minnesota, Minneapolis, Minn.

The influence of dietary fats on the fatty acid composition of atheromatous aorta, blood, liver and depot fat was investigated in 5 groups of 5 rabbits each placed on the following diets for periods of 4 to 6 months: Group I, Purina Rabbit Chow; Group II, Purina Rabbit Chow + 1 per cent cholesterol; Group III, synthetic diet containing 20 per cent safflower oil; Group IV, similar to Group III + 1 per cent cholesterol, and

Group V, synthetic diet containing 20 per cent Hydrol (hydrogenated coconut oil). Groups II, IV and V showed 3- to 7-fold increases of serum total lipids and fatty acids, over Group I, and developed extensive aortic atherosclerosis. Various fatty acids were determined by gas-liquid chromatography. There was great similarity in the tissue fatty acid pattern between Groups I and II and Groups III and IV. The average linoleate concentration of lipids obtained from serum, aorta (intima + media) and diet of Groups I and II was 21, 18 and 40 per cent, respectively, that of Groups III and IV was 43, 37 and 75 per cent, respectively, and that of Group V was 16, 10 and 0.8 per cent, respectively. The concentration of laurate, myristate and shorter chain acids in Group V was 21, 33 and 78 per cent, respectively. This study indicates that plaque fatty acids can be markedly influenced by the type of dietary fats.

FRIDAY MORNING
OCTOBER 21, 1960

KIEL AUDITORIUM

Assembly Hall I

Forrest E. Kendall and O. J. Pollak, Presiding

10:00

44. Comparative Effects of Thyroxin Analogs as Hypocholesterolemic Agents

Maurice M. Best and Charles H. Duncan. From the Department of Medicine, University of Louisville, School of Medicine, Louisville, Kentucky

Several analogs of thyroxin exert a disproportionate effect on cholesterol metabolism of the rat as compared to the naturally occurring L-thyroxin. Four such compounds, tetraiodothyroformic acid (200 to 400 mg. daily), dimethyl-diiodothyroformic acid (200 mg. daily), D-thyroxin (10 mg. daily) and D-triiodothyronine (1 to 2 mg. daily), were selected on the basis of the animal studies and compared to L-thyroxin (0.2 mg. daily) in the hypercholesterolemic human. Fourteen euthyroid patients have been observed continuously for approximately 3 years during which placebos and 2 or more thyroxin-like compounds were administered alternately and their effects on serum cholesterol noted.

Significant reductions of serum total cholesterol resulted from the daily administration of each of the 4 analogs. The reduction was sustained for periods of 16 to 38 weeks of treatment with no tendency to escape. With the substitution of placebos, serum cholesterol returned to the pretreatment range. No tachycardia, weight loss or other evidence of hypermetabolism was observed to result from the drugs, though in 1 patient there was possibly an increase in effort angina. No serious toxic effects were observed, although 3 patients exhibited iodide reactions while receiving 1 of the 2 formic acid analogs. The mean reduction of serum cholesterol resulting from the analogs (20 per cent of pretreatment control level) was somewhat greater than that resulting from L-thyroxin. During the periods of analogue administration mean serum cholesterol was 62 mg./100 ml. below the mean control level of 312 mg./100 ml.

10:15

45. Frequency of Overweight, Obesity, Elevated Blood Pressure and Serum Cholesterol in Railroad Clerks and Switchmen

Henry L. Taylor, Ancel Keys, Henry W. Blackburn, Thomas C. Puchner, and Joseph Brozek, From the Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn.

Examinations of 1,053 clerks and 833 switchmen, between the ages of 40 to 59, were conducted on 32 job sites of 12 railroads operating in the Northwestern area of the United States. For analysis, the subjects were grouped in 3 major geographical areas, i.e., the plains, the mountains and the West Coast. Subjects on the plains were further subdivided into 4 groups according to size of the community. For each area and age-quinquennium group, decile values were determined for relative body weight, obesity (skinfold thickness), systolic and diastolic blood pressure and serum cholesterol. Differences were found between areas in men aged 40 to 49, but not 50 to 59, in skinfolds, relative body weights and systolic blood pressure. The sum of the skinfolds was least in the mountain area, somewhat larger on the West Coast and largest in the Chicago-Milwaukee area. Relative body weights and systolic blood pressures followed a similar pattern, but the differences were smaller and disappeared at an earlier age. The distribution of the several variables between switchmen and clerks were tested at the 50th and 80th centile. No differences were found between switchmen and clerks in any of the variables except in Area A, where switchmen contributed an excess of 20 per cent above both 50th and 80th centile in relative body weight. It is concluded that the clerks do not bring to their jobs an undue proportion of the personal characteristics associated with an increased incidence of coronary heart disease.

10:30

46. Hyperlipemia: Types and Differential Diagnosis

Morton S. Sklarin, Winnifred Seegers and Kurt Hirschhorn. From the New York University Medical Center, New York 16, New York

Hyperlipemia may be defined as an elevation of serum triglyceride. This elevation may be primary or secondary to other disease entities such as diabetes mellitus, nephrotic syndrome, hypothyroidism or biliary obstruction. The primary and many of the secondary hyperlipemias are due to inability to clear ingested fat from the serum adequately. This inability may be due to 1 of 2 possible factors. There may be a total or relative absence of functional lipoprotein lipase. Alternatively, there may be adequate quantities of the normal enzyme present, but the mechanism for activating it is deficient. We have been able to differentiate these 2 mechanisms of hyperlipemia by measuring the response to intravenous heparin. By the use of this method we have established that primary or essential hyperlipemia may be subdivided into at least 2 different disease entities. Each due to 1 of the above mentioned mechanisms.

We have also studied a series of patients with myxedema, all of whom had hyperlipemia and delayed clearing of ingested fat. These patients all responded readily to intravenous heparin, and therefore had adequate lipoprotein lipase, but had a diminished ability to activate this enzyme spontaneously.

Other diseases causing secondary hyperlipemia are now under study.

10:45

47. The Effects of Feeding Fats with Varying Fatty Acid Composition on the Blood and Tissue Lipids of Cebus Monkeys

Robert W. Wissler, Randolph H. Hughes, Lawrence E. Frazier, and Richard A. Rasmussen. From the Department of Pathology, University of Chicago, Chicago, Illinois

Two previous experiments have demonstrated the effects of hydrogenation of food fats upon the blood and tissue lipids of the Cebus monkey (Fed. Proc. 19: 17 (1960). The current experiment included 3 groups of 4 monkeys fed equal quantities of 3 diets which varied only in the lipid components. Butterfat, coconut oil, and corn oil were the fats used, each making up 25 per cent of the ration. The experiment lasted for 45 weeks and the animals were bled, their gall bladders were drained and their livers and adipose tissues were biopsied at 15-week intervals. At each of these intervals they received C^{14} acetate i.v. and they were fed equal daily doses of H^3 cholesterol throughout the experiment. The animals receiving the butterfat and the coconut oil rations each showed a prompt and sustained rise in serum cholesterol (varying from 341 mg. per cent to 418 mg. per cent) while those receiving the corn oil demonstrated less change from the baseline values (256 mg. per cent as compared to 161 mg. per cent). Other serum lipids showed similar trends. Bile acid patterns and the patterns of fatty acids esterified with cholesterol as well as other blood and tissue lipid fractions, will be reported. These will be correlated with the specific activity and synthesis rates of cholesterol in various organs and tissues. Pertinent pathological findings will be correlated with the blood and tissue lipid values and with the tracer data.

11:00

48. An Analysis of the Factors Affecting the "Resting" Free Fatty Acid Level in Normal Man

Robert F. Klein, Morton D. Bogdonoff, E. Harvey Estes and David M. Shaw. From the School of Medicine, Department of Medicine, Duke University, Durham, North Carolina

Plasma free fatty acids (FFA) have been shown to provide a potentially significant source of metabolic substrate for the myocardium in man. Experiments providing these data utilize the technics of arteriovenous differences of FFA across the heart and depend in large part on the serum level during the "resting" state. An analysis has been made of the factors which influence and modulate the "resting" FFA level in man and therefore, in part, the availability of this substrate.

Results of the studies in 69 normal subjects observed in the laboratory in a controlled setting may be summarized as follows: 1) the fasting plasma FFA level in non-obese as well as obese individuals is linearly related to body weight when the effect of fasting is held constant ($p = < 0.05$); 2) the duration of fasting is of itself a direct determinant of the "resting" level ($p = < 0.01$); 3) the duration of fasting influences the direction and magnitude of the change in FFA level following a standardized arousing stimulus ($p = <0.01$).

These variables have been further assessed in a review of the responses to a specific hormonal stimulus (norepinephrine) in 43 subjects. The

marked variability of these curves in part may be dependent on these factors.

These studies provide evidence that the relative availability of an important substrate of the myocardium during the "resting" state is significantly and interrelatedly modified by body size, fasting time, and arousal. These factors, therefore, must be viewed as prior considerations in designing studies of FFA transport and extraction in man.

11:15

49. Specificity of Plasma Fibrinogen Changes for Atherosclerosis

L. O. Pilgeram, A. C. Schram and D. Mills. From the Arteriosclerosis Research Laboratory, St. Barnabas Hospital Research Foundation and the Department of Physiology, University of Minnesota School of Medicine, Minneapolis 4, Minnesota

A 34 per cent increase ($p = 0.01$) in the plasma fibrinogen level has been found in patients who had recovered from the trauma of a myocardial infarction or a cerebral vascular accident for a period of not less than 6 months and who had not received anticoagulant therapy for a period not less than 5 months preceding donation of plasma sample. The interval of time between myocardial infarction or the cerebral vascular accident and analysis indicates (a) that the elevated fibrinogen levels cannot be due to inflammatory conditions or traumatized tissue resulting from the vascular incidents and (b) that the fibrinogen level does not return to normal following a myocardial infarction or cerebral vascular accident. Occlusion of beta- or low-density lipoproteins in the fibrin coagulum did not account for the elevated levels of fibrinogen as was shown by experiments where: (a) known quantities of alpha- and beta-lipoproteins were added to the test system, (b) correction was made for the *occlusion factor*, and (c) the increased yield caused by this occlusion factor represented only a 3.5 per cent increase in fibrinogen yield for as much as a 300 per cent increase in the level of beta lipoproteins.

The data indicate that the fibrinogen level not only increases with age but also superimposes upon the arteriosclerotic an increase in addition to that occurring with increasing chronologic age.

These data support recent reports on the role of fibrin in vascular hypertrophy and atheromatous development. In view of these data, the merit of securing a physiological homeostasis of fibrinogen metabolism prior to the onset of myocardial infarction or cerebral accidents appears to be unquestionable.

11:30

50. The Content of Cephalins in the Plasma of Normal Subjects, Patients with Hyperlipemia and Hypercholesterolemia, and Patients with Coronary Heart Disease

Martin M. Nothman and Samuel Proger. From Tufts College of Medicine, Boston, Mass.

Plasma levels of cephalins, ethanolamine phosphatide and serine were determined by the method of Axelrod, Reichenthal and Brodie in normal subjects, patients with hyperlipemia and hypercholesterolemia and myocardial infarction. These lipids may be important in the clotting mechanism. Ethanolamine phosphatide values ranged between 4.20 and 6.30 mg. per cent and between 10.12 and 21.20 mg. per cent in 6 normal subjects and 11 patients with myocardial infarctions, respectively. Three patients with hypercholesterolemia but without myocardial infarction had values of 10.72, 14.40 and 19.10 mg. per cent, respectively. Values of 16.84 to 28.08 mg. per cent, the highest values in the series, were found in 4 patients who had hyperlipemia, hypercholesterolemia and xanthomatosis, but no myocardial infarction. Serine values ranged from 8.1 to 9.4 mg. per cent, 12.30 to 36.00 mg. per cent and 15.60 to 26.20 mg. per cent in 4 normal subjects, patients with infarction and patients with hypercholesterolemia with infarction, respectively. Here again, patients with xanthomatosis had the highest values: 28.90 to 36.28 mg. per cent. Cephalin values appear to be related to plasma phospholipid concentrations. Ethanolamine phosphatide normally constitutes 2-3 per cent of plasma phospholipids, whereas in the 3 groups above it was 3-8 per cent. Serine normally is 4-5 per cent of plasma phospholipids; it was 5-10 per cent in the 3 groups above. Ingestion of unsaturated fatty acids, which results in a decrease in certain plasma lipid constituents, resulted in a decrease in the cephalins in 5 patients. In 2 patients with xanthomatosis, ethanolamine phosphatide fell from 16.84 to 8.62 mg. per cent and from 28.08 to 10.2 mg. per cent. Serine fell from 28.92 to 14.18 mg. per cent and from 32.16 to 14.60 mg. per cent.

11:45

51. Plasma Heparin Levels. Normal Values and Correlation with Serum Cholesterol and Low-Density Lipoproteins

Hyman Engelberg. From the Cedars of Lebanon Hospital Department of Medicine, Beverly Hills, California

The endogenous heparin(s) content of duplicate 5 ml. aliquots of plasma has been extracted and

biologically assayed by its anticoagulant activity in 256 normal individuals. The range of values was from 10-24 units per cent (1.0-2.4 mg./L plasma). There was little variation in the average values from 10-80 years of age, and there was no difference between the sexes.

Serum cholesterol was measured in 260 individuals who had duplicate heparin determinations on plasma aliquots, and in addition low-density lipoproteins were ultracentrifugally analyzed in 208. The correlation coefficient (r) was obtained for heparin versus cholesterol and heparin versus lipoproteins in both sexes below and over 50 years of age. There was no significant relationship between heparin levels and Standard Sf 0-12 lipoproteins in either sex. All correlation coefficients for heparin vs. cholesterol and heparin vs. Standard Sf 12-400 lipoproteins were negative, i.e., cholesterol and Sf 12-400 lipoproteins decreased as heparin increased. The correlation was definitely statistically significant ($p < 0.01$) in all males, but in females was definitely significant only for the lipoproteins. The coefficients were relatively low numerically. The results indicate that heparin is a regulator of serum lipids and that other factors are also influential.

FRIDAY AFTERNOON

KIEL AUDITORIUM

Assembly Hall II

Aaron Kellner and Campbell Moses, Presiding

2:00

52. Effect of Lipemia on the Disappearance Rate of Intravenously Administered Radioactive Fat

Donald Berkowitz, John J. Spitzer, Millard N. Croll and David M. Sklaroff. From the Albert Einstein Medical Center, Philadelphia, Pa.

The use of intravenous radioactive fat is currently being explored as a new tool to study lipid metabolism. Tolerance tests using 2-3 cc. doses of I^{131}-iodinated triolein have demonstrated that over 75 per cent of the injected fat has already left the circulation after 15 minutes. Although the rate of disappearance is somewhat slower in patients with certain lipid disorders such as essential hyperlipemia and hypothyroid disease, this difference may at times not be very marked.

In an attempt to increase the sensitivity of the procedure, a priming test meal of 250 cc. of light cream was administered orally and the effect of the resulting lipemia noted on the disappearance rate of radioactive fat injected intravenously 2 hours later.

A uniform elevation of the blood radioactivity levels occurred in these instances when compared to corresponding time intervals when the fat was administered in the fasting state. In addition, the disappearance rate of the tagged triolein was much slower thus giving a much more precise distinction between normal and abnormal states. Simultaneous determinations of the blood lipid fractions showed that the amount of radioactivity at any specific time, and its rate of disappearance from the blood was in essence a function of the level of the serum triglyceride concentration.

Further modifications of this pre-feeding principle are in progress in an effort to evolve a simple and rapid intravenous fat tolerance test.

2:15

53. Serum Lipids and Arteriosclerosis in Prostatic Cancer Patients

George F. Meissner and Constance C. Moehring. From the Institute of Pathology, Rhode Island Hospital, Providence, R. I.

In order to test the hypothesis that castration and estrogen therapy in men leads to serum lipid changes accompanied by amelioration of arteriosclerosis, serum lipids were determined periodically in 163 patients with prostatic carcinoma. These were treated for periods of 4 months to 2½ years by orchiectomy and estrogens, which generally resulted in gynecomastia. Twelve of these patients have come to autopsy. Their coronary arteries and aortas were evaluated grossly for the degree of arteriosclerosis and particular attention was paid microscopically to the presence or absence of "early and active" lesions. The gross specimens are being saved for a simultaneous final grading at the conclusion of the study.

To date, it would appear, that there were only slight serum lipid changes and that there was no definite correlation between these and arteriosclerosis found at autopsy, which could be considered a result of castration or estrogen therapy. A series of 10 untreated prostatic cancer patients found at autopsy during the same period of time showed no significant difference as to the degree of arteriosclerosis, when compared to the treated cases.

2:30

54. Serum Lipids in Men Receiving High Cholesterol and Cholesterol-free Diets

William E. Connor, Robert E. Hodges and Roberta Bleiler. From the Department of Internal Medicine, University Hospital, Iowa City, Iowa.

Our previous studies suggested that 1700 to 4800 mg. of dietary cholesterol provided as egg yolk produced marked increases in serum cholesterol. Recently we gave cholesterol as egg yolk in amounts similar to American intakes and compared this with crystalline cholesterol.

Six healthy men, aged 40-49, were given a normal diet one week and subsequently formulae, each providing 3000 calories, 70 Gm. protein and 133 Gm. fat. The fat was a vegetable oil mixture with saturated fatty acid composition similar to egg yolk. The iodine numbers for all periods were 84-86. The experimental periods of 3 weeks each were: I (cholesterol-free), II (egg yolk providing 475, 950 and 1425 mg. of cholesterol for respective pairs of men), III (cholesterol-free); and IV (crystalline cholesterol, 1200, 2400 or 3600 mg.). During the egg yolk feeding, 11 to 33 Gm. of the total fat was derived from egg yolk.

The mean serum cholesterol decreased 57 mg. per cent ($p < 0.01$) during the first cholesterol-free period (I). The addition of egg yolk (II) led to an increase of 68 mg. per cent ($p < 0.001$). No differences occurred among the 3 cholesterol intakes. With the second cholesterol-free formula (III), the serum cholesterol decreased 55 mg. per cent ($p < 0.001$). Serum phospholipids varied with the serum cholesterol. In period IV crystalline cholesterol increased the serum cholesterol 18 mg. per cent.

In diets equivalent in amounts and composition of fat, the addition or subtraction of moderate amounts of cholesterol as egg yolk caused significant changes in serum cholesterol concentrations.

2:45

55. Vascularization of In Situ and Intraocularly Transplanted Atheromatous Plaques in Rabbits

A. C. Higginbotham and F. H. Higginbotham. From West Virginia University School of Medicine, Morgantown, W. Va.

Vascularization of atheromatous plaques is commonly believed to occur either late in atherogenesis, or to occur early and perhaps play an important role in extension of the plaques as well as in their formation. Observations on in situ and intraocularly transplanted plaques in rabbits, and on a limited amount of human material, suggest that in general both views may be true, but in a more restricted sense vascularization should be included with the processes occurring early in atherogenesis.

A well developed plaque in the rabbit is seldom of uniform composition. The deeper and more central parts generally are more fibrous or degenerative compared with superficial and circumferential parts which are more cellular, containing numerous foam cells. Vascularization of such a transplanted plaque apparently is restricted to the more cellular portions, since no vessels have been found in the degenerative areas.

In the rare instances when small vascularized areas of old atheromatous plaques in situ were seen in the aortas of rabbits several months after their production, the vessels were limited to areas containing foam cells. The same relationship appears to exist in the human arteries examined.

Since there seems to be a definite relationship between foam cells and vascularization of plaques, the process should more properly be consdered as one occurring early in plaque formation, but which may occur later in old plaques whenever accumulations of foam cells are present.

3:00

56. Biochemical Studies in Full-Blooded Navajo Indians. II. Lipids and Lipoproteins

Robert J. Kositchek, Moses Wurm and Reuben Straus. From the Saint Joseph Hospital, Burbank, Calif.

Epidemiological studies of primitive ethnic groups have implied the presence of some genetically determined protective mechanisms, amongst other factors, to account for the low incidence of coronary heart disease. This has been the case in the Navajo Indian, presumably subsisting on a "typical American diet." Since we have shown that elevated globulins in the Navajo Indian is not genetically determined and probably not related to the low incidence of coronary heart disease, further studies were made of the blood lipids.

Random early morning blood samples were collected in the interior of the Reservation from 30 full-blooded Indians having a mean age of 48 years. Standard lipid analyses, including paper lipoprotein electrophoresis, revealed strikingly low individual and mean values. With the exception of 3 elevated values found in lipemic specimens knowingly taken postprandially, the beta/alpha lipoprotein ratios ranged between 0.38 to 2.33 (mean 1.49), which, as an index of atherogenesis, correlates with the general absence of coronary heart disease.

Statistical comparison of this data with that in 3 control populations: "normals," patients with manifest atherosclerosis, and tuberculous patients, showed significantly lower cholesterol concentrations, C/P ratios and beta/alpha ratios.

Preliminary observations of dietary habits revealed that although the Navajo Indian may consume foods rich in fat, the quantity is markedly restricted by availability and modified by unique preferences so as not to be considered a "typical American diet." It is concluded that the general absence of coronary heart disease in this ethnic group is a product of their low caloric diet, together with an unimpaired lipid metabolism and that this is reflected by a low beta/alpha lipoprotein ratio.

3:15

57. Coronary Arterial Calcification

David H. Blankenhorn. From the University of Southern California, School of Medicine, Department of Internal Medicine, Los Angeles, Calif.

Coronary arterial calcifications are the most common radiopaque lesion of the heart. Although improved radiologic techniques now lead to discovery of an increased number of coronary arterial calcifications in living man, the prevalence of these lesions is frequently underestimated at autopsy. Autopsy study of the radiographic pattern of coronary arterial calcification in 89 adults indicates that a unique situation exists in this artery. Calcification invariably occurs in atheromatous lesions and Monckeberg's medial calcification does not exist. Massive coronary calcification is most frequently seen in hearts exhibiting grossly dilated coronary arteries and it seems possible that dilation effects tolerance to severe atherosclerosis, permitting survival for a sufficient period to allow extensive calcification. Small calcifications of the coronary have been found in young men (aged 30 to 50) dying suddenly of ischemic heart disease. These men apparently could not tolerate coronary atherosclerosis for a sufficient period to develop extensive calcification. These findings are relevant to the design of experiments investigating the prevalence of atherosclerosis by search for manifest ischemic heart disease, because they demonstrate certain individuals in whom the extent of atherosclerosis is inversely proportional to the clinical significance of lesions. These findings also indicate that small calcifications discovered in a young man have much greater significance than extensive calcification at a later age.

3:30-3:45 Intermission

3:45

58. Prognosis and Serum Lipids in Survivors of Myocardial Infarction

Robert D. Roe, Alick Little and Henry M. Shanoff. From the Sunnybrook Hospital, Department of Veterans Affairs, Toronto, Ontario, Canada

Previous studies, from this and other centres, have shown that patients with coronary heart disease have higher average serum lipid levels than controls. The present paper, restricted to the study of survivors of myocardial infarction, examines the relationship between prognosis and the concentration of serum lipids.

Cumulative survival curves were calculated in 120 male patients age 30-80. They were free of hypertension, secondary hypercholesterolemic states, including diabetes mellitus, and other complicating diseases. The serum lipid fractions determined at the initial examination and annually thereafter, included total cholesterol and standard Sf lipoproteins 0-12, 12-20, 20-100 and 100-400.

The overall 5-year survival from the time of the initial visit is 60 per cent. Each lipid fraction was studied separately. Those men with values above the means for their individual decade were compared with those with values below. The cumulative survival curves in the 2 groups were identical. The results were similar for all lipid fractions studied, whether initial readings only or the means of several readings were used and whether survival was calculated from the first myocardial infarction or from the first examination for this study.

The results indicated that once myocardial infarction occurred, there was no relationship between survival and the concentrations of serum total cholesterol and the standard Sf lipoproteins.

4:00

59. Interrelation of Coronary Occlusion, Intercoronary Anastomosis, Myocardial Infarction and Angina Pectoris

Robert B. Allison, Felix L. Rodriguez, Walter H. Abelmann and Laurence B. Ellis. From the Boston City Hospital, Boston, Mass.

An unselected series of 250 hearts was studied at the Boston City Hospital by a modified Schlesinger's coronary injection technique, combined with meticulous exploration of the myocardium. Independently, the clinical records were reviewed for clinical evidence of coronary artery disease.

The average age was 68.1 years. There were 138 men and 112 women, 210 whites and 40 Negroes.

Fifty-seven of 58 hearts with 1 or more major

coronary occlusions showed intercoronary anastomoses, which were found in only 13 per cent (2 of 15) of normal hearts. Blumgart's contention that intercoronary anastomoses can completely protect the myocardium from infarction, although disputed by others, was confirmed. Ten isolated coronary artery occlusions without myocardial infarction were found and in each extensive intercoronary anastomoses existed.

Seventy-two (29 per cent) of the hearts showed 115 myocardial infarcts. Twenty-one per cent of these infarcts were not associated with coronary occlusions and were characterized as a group by being small, healed, not accompanied by angina, and clinically not evident.

Twenty-five of 27 angina patients had coronary occlusions or myocardial infarcts or both. The number of occlusions per heart in patients with occlusions, with or without angina did not differ.

False positive clinical diagnosis of definite myocardial infarction was uncommon (4 of 29, or 14 per cent) but 40 per cent (29 of 72) of pathological myocardial infarctions were clinically not diagnosed. When the clinical diagnosis of definite coronary artery disease was made, occlusion or severe stenosis of the coronary arteries was found at autopsy in 37 of 43 cases (86 per cent).

4:15

60. The Frequency of Coronary Thrombi as Related to the Duration of Survival from the Onset of Acute Fetal Episodes of Myocardial Ischemia

David M. Spain and Victoria A. Bradess. From the Beth El Hospital, Brooklyn, N. Y.

Over 1000 consecutive autopsies on sudden or relatively sudden deaths from coronary atherosclerosis with acute myocardial ischemia were analyzed for fresh and recent coronary thrombi. Of these 368 were witnessed so that the duration of survival from the onset of the acute episode was known. Similarly studied were 200 consecutive autopsies on hospital deaths from acute myocardial infarction who had survived at least 24 hours from the onset of the acute episode. The cases were divided into 3 groups; those that had survived less than 1 hour; 1 hour to 24 hours; and over 24 hours. Fresh or recent coronary thrombi were found in 49 (16 per cent) of 303 cases that had survived less than 1 hour; in 24 (37 per cent) of 65 cases surviving 1-24 hours; and in 109 (54 per cent) of 200 surviving over 24 hours.

There was an increased frequency of fresh thrombi with an increase in the duration of survival from the onset of the acute episode. These findings would indicate that coronary thrombi may perhaps play only a secondary role in the precipitation of acute myocardial ischemic episodes. The therapeutic implications of this will also be discussed.

4:30

61. Clinicopathologic Study of the Feasibility of Direct Surgical Treatment for Occlusive Coronary Artery Disease

Harry A. Swedlund, Richard W. P. Achor, and Jesse E. Edwards. From the Mayo Clinic and the Mayo Foundation, Rochester, Minn.

The coronary arteries of 112 patients with an antemortem diagnosis of coronary-artery disease were studied at necropsy with regard to the feasibility of coronary endarterectomy for direct relief of the luminal narrowing. The size of the main arteries, length of their obstructive lesions and degree of patency of the small peripheral branches were analyzed. Each heart then was classified as being theoretically eligible for operative correction, susceptible to palliation only, or inoperable. The condition was judged as theoretically operable in 20 cases (18 per cent), as capable of palliation in 58 cases (52 per cent), and as inoperable in 34 cases (30 per cent). Various clinical features (age, sex, angina pectoris, hypertension, diabetes, cardiomegaly and a history of myocardial infarction) were analyzed in an attempt to find any factors that might suggest a more favorable anatomic state of the coronary arteries in a given patient. No correlation could be discovered in this series. The youngest man judged operable was 54 years of age; of 26 men less than 60 years of age, 2 were considered operable and 12 capable of palliation. Of the 4 women below age 65, none were considered operable and only 2 were thought to be capable of palliation. In this study, it appeared that the more severe and diffuse coronary-artery disease was present in the younger male patients. The possibility of selecting by clinical means those candidates with occlusive coronary-artery disease who might be amenable to direct surgical attack on the arteries is not encouraging at this time.

TO BE READ BY TITLE

62. Immunological Studies in Atherosclerosis. I. The Relationship of Certain Immunochemically-Defined Serum Protein Moieties to Serum Lipids, Weight and Blood Pressure in Myocardial Infarction

Saul P. Baker, A. S. Markowitz and Alvin Dubin. From the Chicago Medical School and Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, Illinois

Immunological differentiation of sera from patients with myocardial infarction (presumptive evidence of coronary atherosclerosis) from control subjects utilizing quantitative precipitin techniques has previously been reported.

Subsequently, 101 patients with myocardial infarction have been evaluated to date with regard to protein moieties specific to 3 ultracentrifugally-defined serum β-lipoprotein fractions: Fraction I (S_f 10-100, peak S_f 25); Fraction II (S_f 5-15, peak S_f 9); and Fraction III (S_f 3-9, peak S_f 6). Serum lipids, weight, and blood pressure were concomitantly determined. Thirty-five control subjects were similarly evaluated.

In the infarcts, a mean of 2.76 mg. per cent protein nitrogen (range 0.82 to 5.36) was obtained for Fraction I; a mean of 0.91 mg. per cent (range 0.11 to 3.00) for Fraction II; and a mean of 2.92 mg. per cent (range 0.25 to 5.50) for Fraction III. The controls yielded a mean of 0.87 mg. per cent protein nitrogen (range 0.27 to 2.68) for Fraction I; 0.36 mg. per cent (range 0.11 to 0.94) for Fraction II; and 0.73 mg. per cent (range 0.12 to 2.38) for Fraction III.

Total serum lipids, lipid phosphorus, total serum cholesterol, esterified cholesterol, cholesterol/lipid phosphorus ratio, systolic and diastolic blood pressure demonstrated higher mean values in the infarcts, while mean weight was somewhat higher in the controls. However, *for the individual,* there was *no correlation* between any of the protein fractions measured and any of the serum lipids, weight, or blood pressure.

It is, therefore, suggested that quantitative immunochemical studies of protein moieties specific to fractions of ultracentrifugally defined human serum β-lipoproteins may be useful in evaluating pre-clinical coronary atherosclerosis in man, particularly in those *individuals* in whom the usual parameters of atherogenesis are within normal limits.

63. Immunological Studies in Atherosclerosis. II. The Effect of Passive Immunization with Polyvalent Anti-Human β-Lipoprotein Antiserum on Serum Lipids, Proteins and Atherosclerosis in Cholesterol Fed Rabbits

Paul P. Baker, A. S. Markowitz, Paul B. Szanto and Alvin Dubin. From the Chicago Medical School, and Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, Illinois

Active immunization of rabbits with β-lipoproteins from cholesterol fed cocks has been reported to inhibit development of atherosclerosis subsequently induced by cholesterol feeding in these rabbits.

Accordingly, 12 New Zealand white male rabbits were divided into 2 groups of 6 each. Six were then injected with 4 ml. each of a polyvalent anti-human β-lipoprotein rabbit antiserum prepared individually to each of 4 β-lipoprotein fractions and then pooled prior to injection. The 6 controls were concomitantly injected with 4 ml. each of pooled normal rabbit serum. All 12 rabbits were then placed on a 2 per cent cholesterol diet. They were maintained on this diet for 8 weeks and then sacrificed. Four milliliter injections of either polyvalent antiserum or normal rabbit serum were administered at bi-weekly intervals during cholesterol feeding.

Serum total lipids, lipid phosphorus, total cholesterol, per cent esterified cholesterol and β-lipoproteins increased markedly in all rabbits. Total proteins and albumin/globulin ratio demonstrated little change, except for a hypoalbuminemia of 2.9 gm. per cent in 2 rabbits. Gamma globulin was variable and rose in half of each group. No inhibition of atherosclerosis was observed in this experiment. The 2 rabbits demonstrating the most severe aortic involvement were found in the immunized and control groups, respectively, having total serum lipids of 3741 and 3240 mg. per cent, with cholesterols of 2550 and 2220 mg. per cent, respectively.

It is, therefore, concluded that passive immunization with anti-human β-lipoprotein antiserum exerts no apparent effect upon serum lipids, proteins and the development of atherosclerosis in cholesterol fed rabbits.

64. Comparison By Gas-Chromatography of the Fatty Acid Content of Adipose Tissue with Dietary Intake of Fat in Vegetarian and Non-Vegetarian Males

J. Gordon Barrow, Carroll B. Quinlan, Robert E. Edmands, Virginia S. Whitner and Mary Helen R. Goodloe. From the Emory University School of Medicine, Atlanta, Georgia

Dietary studies of Trappist vegetarian and Benedictine non-vegetarian monks indicate that they differ significantly in the percentage of calories which they derive from fat. (Trappist: 25 per cent, Benedictine: 45 per cent).

Biochemical studies comparing the vegetarians with the non-vegetarians reveal that most serum lipids are significantly lower in the former group.

Adipose biopsy specimens were obtained in 33 members of both groups who were in the same age group and had consumed their respective diets

for 3-10 years. The fatty acid composition of the adipose tissue was analyzed with gas-chromatography. This was compared with dietary fatty acid intake obtained via repetitive diet records on each individual. Comparing the fatty acid composition of the adipose tissue with the fatty acid composition of the dietary intake, there appears to be a moderaet correlation between these 2 with the linoleic acid showing the best correlation.

65. The Relation of Fat Tolerance to Coronary Atherosclerosis

Donald Berkowitz, David M. Sklaroff, John J. Spitzer and William Likoff. From the Albert E. Einstein Medical Center, Philadelphia, Pennsylvania

Considerable attention is being focused on hypercholesterolemia as an important factor in the genesis of atherosclerosis, and many regimens, both dietary and drug, are being advocated in an attempt to normalize cholesterol levels.

On the basis of more precise methods for studying lipid metabolism, notably radioactive fat tolerance tests, evidence is at hand which indicates that abnormal fat tolerance is more frequently present, and that this may represent a more fundamental disturbance than that reflected by an elevated blood lipid fraction. Furthermore, treatment of patients with coronary artery disease and hypercholesterolemia with various of the cholesterol-lowering agents such as nicotinic acid, sitosterol and triparanol, has resulted in a reduction in the cholesterol level in a certain per cent of those treated with no concomitant improvement in the fat tolerance. We do not believe it likely, therefore, that these drugs produce any favorable changes on the atherosclerotic process.

Attempts to improve fat tolerance by weight reduction, heparin and certain other related preparations, with or without a simultaneous lowering of the cholesterol, would appear to be a more rational approach to the problem.

66. The Effect of Commercial Margarines on Plasma Cholesterol Levels

J. M. R. Beveridge and W. F. Connell. From the Department of Biochemistry, Queen's University, Kingston, Ontario, Canada

The effects on plasma cholesterol levels of 8 commercial margarines were determined under 2 regimens utilizing homogeneous diets. In 1 experiment 95 university students were placed for 8 days on a ration providing 22.5 per cent of calories from butter. The subjects were divided into 10 groups and for another 8 days consumed a diet modified by the addition of 22.5 per cent of calories from fat at the expense of the carbohydrate moiety. Besides the groups on the 8 margarines, 1 group was given butter and another, corn oil. The butter ration led to a significant increase in plasma cholesterol but there was no significant change noted with any of the margarines nor with the corn oil. The greatest decrease was, however, observed in the latter instance. In the second experiment 97 university students ate a fat-free formula ration for 8 days. The subjects then were divided into 10 groups and for another 8 days they ate a diet in which 45 per cent of calories from fat were provided at the expense of the carbohydrate moiety. The butter led to a highly significant increase in plasma cholesterol and the corn oil to a significant decrease. In the case of 6 of the margarines, no change from the level noted on the fat-free diet was found. However, 2 of the margarines did lead to a significant increase although this was less than half that observed on the butter fat diet.

67. New Methods of Serum Glyceride Analysis

David H. Blankenhorn. From the University of Southern California School of Medicine, Department of Internal Medicine, Los Angeles 33, California

The glyceride fraction of serum lipids has been shown to play an important role in energy metabolism and to affect blood oxygen transport. It also may affect blood coagulation. This paper will present an improved system of blood glyceride analysis. To find patients with abnormal blood glycerides a screening technic has been devised. This is a modification of the total cholesterol determination of Abell, Brodie, Levy and Kendall which allows concurrent total cholesterol and total lipid determinations. When total cholesterol and total lipids are known the lower limit of serum glyceride content can be estimated. To furnish further information, a simple microchromatographic method employing Florisil has been devised. This technic permits determination of total glycerides, triglycerides, diglycerides and monoglycerides in 1 cc. of serum. The absorbent properties of Florisil have been found to be constant from lot to lot and to effect sharp separation of lipid classes. Ninety-seven to 99 per cent recovery of added glycerides can be achieved. The existence of monoglycerides and diglycerides in human blood can be demonstrated with this system.

68. The Effect of Nicotinic Acid, Stearic and Linolenic Acid, Heparin, Estrogenic Hormones on the Uptake and Dispersal of Cholesterol in Aortic Endothelial Cells Grown in Tissue Culture

Ancel U. Blaustein and Marilyn Rosenblat. From the New York Medical College, New York, New York

Rat aortic endothelial cells were grown in tissue culture according to the method described by Lutstein, et al. When sufficient explantation occurred transplants were placed in a double cover slip Maximow slide. Groups of cells were exposed to a media containing serum derived from patients whose cholesterol levels ranged from 350-560 mg. per cent. On the third day under bright light or phase microscopy lipid deposits were seen in the cell cytoplasm. As exposure to cholesterol continued, a marked increase in uptake was demonstrated by Sudan Black B stains and specifically by the Lieberman-Burchard reaction.

The following experiments were performed.

1. Nicotinic acid (5 per cent) plus high cholesterol serum were added to the feeding media. Explant cells were exposed to the composite media in Maximow slides for 2 weeks. The media was changed every third day.

2. Linolenic acid plus high cholesterol were added to the feeding media as above for 1 week.

3. Cells were exposed to stearic acid and high cholesterol as with linolenic acid.

4. Heparin and high cholesterol serum were added to the feeding media and cells exposed to the composite mixture.

5. Conjugate estrogens were added to the media, in addition to high cholesterol serum. The cells were exposed to this mixture.

Five per cent nicotinic acid appreciably decreases the uptake of cholesterol by the cells. It also causes the dispersal of lipid from cells already laden with it. Linolenic acid limits the uptake of cholesterol while stearic acid enhances it. Estrogens and heparin do not influence uptake or dispersal of cholesterol.

69. Serum Free Cholesterol and Atheroma in Young Cockerels

Clyde T. Caldwell. From the Upjohn Company, Kalamazoo, Michigan

Studies of free to combined cholesterol conversion resulting from the incubation of sera from normal and cholesterol-fed young cockerels show a relationship between the amount of cholesterol that remains uncombined and the degree of atherosclerosis. The per cent of original free cholesterol not combined after 30 hours' incubation of sera from 21 groups of birds increased without overlapping from normal (17 to 45) through mild, spontaneous (45 to 56) and severe induced atherosclerosis (56 to 87). Absolute mg. per cent values for these per cent ranges were (4.7/27.2 to 10.9/24.4), 12.0/26.5 to 12.7/22.8), and (33.7/59.5 to 78.4/90.2), respectively. Corresponding mean values for uncombined cholesterol were 9, 14 and 67 mg. per cent, while 17, 13 and 23 mg. per cent were combined. Total cholesterol values were essentially unchanged.

Artery involvement was always found when more original free cholesterol remained than was combined upon incubation. It is noteworthy also that the small range between 45 and 56 per cent uncombined was sufficient to differentiate between normal and severely atherosclerotic birds.

A large increase above normal amounts of free cholesterol not combined in the severely atherosclerotic (from 9 to 67 mean mg. per cent) was a characteristic incubation difference found between normal and severely atherosclerotic serum. However, only a small increase (from 17 to 23 mg. per cent) was shown by corresponding mean values for free cholesterol converted to the combined form.

70. Influence of the Dietary Lipids on the Carbohydrate Tolerance in Diabetes and Pre-Diabetes

Mario Campagnoli, Juan M. Castagnino and Rosa L. de Caneda. From the National Institute of Nutrition, Ministry of Public Health, Buenos Aires, Argentina.

Recent studies on the effects of dietary lipids upon the arteries have led to widespread reduction of these nutrients in many disease states. There has lately been some speculation as to whether the diabet's diet—from the viewpoint of his arteries—should be: a) low in total fat, or b) rich in fat provided the saturated fatty acids are kept low. This study was designed with the double purpose of ascertaining the long-term effect of a diet rich in fats of the unsaturated type on: a) the carbohydrate tolerance evaluated through the insulin requirements and b) the arterial system. Participating in the experiment diabetic patients at the "Instituto Nacional de la Nutricion" (National Institute of Nutrition), the controls ate the regular diet containing about 80 grams of fat a day, half saturated and half unsaturated. The patients in the study received isocaloric diets containing about 120 grams of fat, of which at least 80 grams were provided by grape-seed oil, widely consumed in this country. The results may be summarized as follows:

1) Carbohydrate tolerance improved. In the

diabetics of the juvenile type, hypoglycemia was less severe and less frequent.

2) Arterial lesions did not progress. In some cases regressions occurred of the retinal changes.

3) The large amounts of oil were easily incorporated into the foods and readily accepted by the patients.

4) This type of diet proved practical and useful in the treatment of diabetes especially from the viewpoint of prevention of atherosclerotic changes.

71. Cholesterol Synthesis in Human Blood Vessels

Aram V. Chobanian and William Hollander. From the Evans Memorial Hospital, Boston, Massachusetts

Recent radioisotopic studies in our laboratory have indicated that significant exchange takes place between serum and blood vessel cholesterol in human subjects. The present investigation was undertaken to determine whether any other mechanism might be involved in the accumulation of cholesterol in the arterial wall.

Segments of human arteries removed at the time of surgery for aortic vascular disease or for limb amputations have been incubated in media containing C-^{14}-labelled precursors of cholesterol, C^{14} acetate and C^{14} mevalonic acid. The rate of formation of C^{14}-labelled sterols in the arterial wall has been followed over a 3-24 hour period. The results indicate that significant synthesis of cholesterol from both labelled precursors occurs in the human arterial wall studied *in vitro*. The sterol radioactivity does not appear confined to a single area but is present in both the intima and the outer layers of the arteries studied.

In conclusion, significant synthesis of cholesterol occurs in the human arterial wall. The findings suggest that the accumulation of cholesterol in the blood vessels may result from both an exchange with serum cholesterol and a synthesis of cholesterol in the vessel wall.

72. The Lipid Composition of Serum Lipoproteins in Health and Coronary Artery Disease

Louis Cohen, Karam V. Batra and Richard J. Jones. From the Department of Medicine, University of Chicago Clinics, Chicago, Illinois

Whole serum and 3 ultracentrifugally separated serum lipoprotein fractions [densities < 1.019 (S_f 12-400), 1.019-1.063 (S_f0-12), > 1.063 (HDL)] obtained from 13 healthy males and 13 patients with coronary artery disease (7 normo- and 6 hypercholesterolemic) were analyzed for total (TC), ester (EC) and free (FC) cholesterol. The latter 2 sterols were separated by alumina chromatography. All colorimetric tests were performed using the Fe Cl_3-H_2SO_4 color reagent.

The following observations were made: 1) in health, the EC:FC ratio of whole serum is 2.17 ± .106 (standard error) and in lipoproteins of density < 1.019 is 1.43 ± .128, significantly less than that found in the 2 heavier density fractions, which were 2.27 ± .154 and 2.94 ± .322, respectively 2) EC:FC relationships, statistically similar to that found in health, exists in whole serum and the serum lipoproteins in the 2 patient groups; 3) the mean total cholesteral of lipoproteins of density < 1.019 was 36 mg./100 ml. serum in each of the 2 patient groups, significantly greater ($p < 0.01$) than found in health, 24 mg./100 ml. serum; and 4) the EC:FC ratio in lipoproteins of least density is the same as reportedly found in early atheroma

These data indicate the association of ester and free cholesterol with lipoproteins of density <1.019 is unique in both health and coronary artery disease; that lipoproteins of density < 1.019, in contrast to heavier lipoproteins, may correlate best with the presence of coronary artery disease; and suggest the possibility that lipoproteins of least density may selectively enrich the intima.

73. The Effect of Unsaturated Fat on the Serum Cholesterol Level of Cholesterol-Fed Rabbits

William S. Collens and Gerald B. Dobkin. From the Maimonides Hospital, Brooklyn 15, New York

Increases in the level of circulating cholesterol have been regarded by some investigators as playing a part in the genesis of atherosclerotic disease. This had led to a series of studies in which it was shown that the dietary use of fats containing unsaturated fatty acids could result in lowering serum cholesterol levels. As a result of this work, unsaturated fats have been regarded as potential therapeutic agents in the control of atherosclerotic disease.

In the present studies the blood cholesterol of rabbits maintained on feed containing 2 per cent cholesterol was studied. The rise which followed this daily feeding, compared with a control group, will be shown graphically. When 2 per cent cottonseed oil was added to the cholesterol-feed formula, the rise in the rabbit serum cholesterol was strikingly increased above the cholesterol-fed rabbits, frequently by a 5-fold factor over the previous level. Controls with 2 per cent cottonseed oil-feed mixtures failed to increase the serum cholesterol. The implications of this study show reasonable doubt as to the value of unsaturated fatty acids when added to a cholesterol-feed diet in the experimental animal.

74. Advanced Atherosclerosis of the Human Type in the Rabbit: A New Experimental Tool

Paris Constantinides, John Booth and Glen Carlson. From the Anatomy Department, University of B. C., Vancouver, B.C., Canada

It is the main argument against the "lipogenic" theory of the origin of atherosclerosis that while the experimental exposure of mammalian arteries to lipemia causes intimal foam cell accumulations resembling some types of very early human lesions (the so called "fatty streaks"), it has never yet reproduced the advanced stages of the human disease (capillarised plaques with thick collagenic capsule and calcified gruel) or any of its complications (hemorrhage, ulceration, thrombosis). Thus, the human applicability of pharmacological data derived from animal experiments involving cholesterol atherosclerosis has been generally questioned. The present study shows that rabbit cholesterol lesions will develop all the features of the advanced human disease when they are allowed to age for 2 years after establishment, and that they can develop all human complications in addition to advanced characteristics when exposed to intermittent lipemia and other insults during aging for only 8 months.

The above findings provide strong support for the "lipogenic" theory of the pathogenesis of human atherosclerosis. While they do not exclude additional other etiologies for human plaques, they demonstrate that typical human disease can evolve from simple intimal lipid deposits under proper conditions.

75. Cholesterol Biosynthesis Inhibition by Triparanol (MER-29)

Elmer E. Cooper. From San Antonio, Texas

Among the therapeutic attempts to lower serum cholesterol inhibition of biosynthesis at the liver level using MER-29 has been investigated.

Thirty-six subjects with and without atherosclerotic disease have been given this drug from 1 to 5 months at an oral dosage of 250-750 mg. per day. The average control was determined from 3 separate tests taken at weekly intervals. Follow-ups during medication were taken every 2 weeks. Analyses were done by the same technician using the Bloor colorimetric method. There were no dietary restrictions.

Thirty-three of the 36 subjects had an appreciable reduction of serum cholesterol ranging from 23 to 122 mg. per cent or 8 to 43 per cent of control values.

Depressions in cholesterol occurred within 1 week and progressed to their maximum drops in 4 to 6 weeks. These lowered levels were maintained throughout the study with only slight variations. Within 2 weeks after medication was discontinued, the cholesterol levels rose to control values. Repeat courses of medication reproduced similar lowering of cholesterol levels.

No toxic effects were observed in hematopoietic, cardiovascular or renal systems. Serum bilirubins, urobilinogens, alkaline phosphatases and transaminases (SGOT) were all normal. Cooperation and tolerance were excellent. In 1 instance, there was an evanescent erythematous rash.

76. The Treatment of Hypercholesterolemia with Thyroid Analogues in Patients with Coronary Artery Disease

Eliot Corday, David W. Irving and Henry Jaffe. From the Cedars of Lebanon Hospital, Los Angeles, California

The hypocholesterolemic action of the thyroid analogues tetraiodothyroformic acid (T_4F), triiodothyroproprionic acid, and sodium dextrothyroxin have been studied in 56 patients for a period of 1 year. Most of these patients were previously made hypothyroid with I^{131} because of severe coronary artery disease and all had hypercholesterolemia. The patients were unable to tolerate normal doses of thyroid medication because of adverse metabolic and adrenergic effects. Serum cholesterol levels were obtained every 2 weeks. Placebos were first administered for a 2-to 12-week period, then the thyroid analogue was given and the patients observed for a further 12-month period. The drug was stopped and restarted several times to prove that the reduction was due to the agent.

The thyroid analogues showed a marked hypocholesterolemic effect. In the T_4F series of 26 patients, the average control cholesterol was 372 mg. per cent and the average reduction was 148 mg. per cent (a drop of 33 per cent). Equally effective results were noted in the triiodothyroproprionic acid group.

These thyroid analogues have minimum metabolic or adrenergic effects and are effective in lowering serum cholesterol levels in brittle coronary patients.

77. Substances Modifying Gel Rates of Fibrinogen-Thrombin

Herbert L. Davis and Nora L. Davis. From the University of Nebraska College of Medicine, Omaha, Nebraska

Recalcification times of ACD plasmas may be altered by representatives of 4 classes of substances. These appear to function by affecting the colloidal stability of fibrinogen. Coagulants decrease the negative charge on fibrinogen or they reduce its water-binding power; anticoagulants increase the charge or they augment the bound-water aspect of its stability.

Now it has been found that gels produced from fibrinogen plus thrombin are affected similarly and at comparable reagent concentrations. Fibrinogen-reagent and thrombin-saline are incubated in separate tubes, and mixed for gel formation.

Gel times are reduced by cationic agents such as protamine, toluidine blue or Polybrene. Gel times are reduced, also, by reagents which decrease the water-binding of fibrinogen, such as phospholipids, soaps, alcohols, Stypven, Premarin, Adrenosem or Tachostyptan. With both series, optimum amounts of reagent produce minimum gel times, and excess concentrations retard or prevent gel formation. The degree of acceleration produced tends to be less than was previously found for the same reagents added to whole plasma, but doubling the rate is possible.

Anticoagulants of anionic nature increase gel times and include heparin and Mepesulfate (heparinoid). Strongly hydrated colloids such as dextran and albumin give less consistent results in these component systems. Antagonisms have been demonstrated by incubating fibrinogen in the presence of heparin-Polybrene, heparin-Premarin, heparin-sodium stearate, and other combinations. Such findings suggest that in plasma and *in vivo* relevant useful substances may act directly on fibrinogen to alter the rate of blood clotting.

78. Intravenous I-131 Triolein Tolerance Curves in Patients With Diabetes Mellitus and Myocardial Infarction

Edward R. Dickstein, Leonard J. Feinberg, Samuel Bellet and Herschel Sandberg. From the Philadelphia General Hospital, Philadelphia, Pennsylvania

Previous studies from this and other laboratories have demonstrated that oral I^{131} triolein tolerance curves in patients with coronary artery disease and diabetes mellitus differ significantly from those of normal controls. The radioactivity in the whole blood and its circulating lipoprotein fraction is elevated in these conditions compared to that found in normal controls. In order to evaluate the relative importance of absorption in producing these effects, this metabolic aspect has been by-passed by using the intravenous route for the administration of the labelled triolein. Twenty-six subjects were employed in this study: 10 with diabetes mellitus; 6 with myocardial infarction; 10 served as a control group.

The I^{131} triolein, freshly emulsified and sterilized by pressure filtration, were administered intravenously to these individuals and serial blood samples were drawn in rapid succession for the first 10 minutes and less frequently thereafter for 3 hours. Twentyfour hour samples were also obtained. The radioactivity in the whole blood and its circulating lipoprotein fraction (determined by precipitation with trichloracetic acid) were evaluated in a manner previously described. It was found that 6 of the 10 diabetic subjects displayed a delay in the clearance of lipid from the blood stream. No significant difference was found between the control population and the subjects with myocardial infarction. No correlation could be drawn between the delay in the clearance of radioactivity in the diabetic subjects and parameters such as serum cholesterol, daily insulin dosage, age, weight or sex.

79. I-131 Oral Triolein Tolerance Curves in Elderly Patients With Coronary Artery Disease

Jerry Edelman, Herschel Sandberg, Edward R. Dickstein and Samuel Bellet. From the Philadelphia General Hospital, Philadelphia, Pennsylvania

Earlier studies have demonstrated that middle-aged subjects with documented evidence of myocardial infarction metabolize orally administered I^{131} triolein in an abnormal manner. Following the ingestion of a labelled test meal the radioactivity in the whole blood (WB) and its circulating lipoprotein fraction (TCA) reaches higher levels and remains elevated for at least 24 hours compared to those of a control population. In patients with diabetes mellitus, similar abnormalities were also found, particularly in patients with atherosclerotic complications.

These abnormal curves failed to appear, however, in diabetics over 60 years of age. It was therefore decided to study oral I^{131} triolein tolerance curves in elderly individuals with coronary artery disease.

Twenty-five subjects with clinical and electrocardiographic evidence of coronary artery disease were utilized in this study. Ten were 60 years of age or older; 15 were under 60 years. The I^{131} triolein test meal was administered to these individuals and serial blood samples were drawn and analyzed for radioactivity in the whole blood (WB) and trichloracetic acid precipitable fraction (TCA) in a manner previously described. In several instances serum cholesterols and phospholipids were also determined.

The peak whole blood activity (WB), circulating lipoprotein activity (TCA) and fraction of total blood activity precipitable with trichloracetic acid (TCA/WB) were considerably higher in the younger subjects than in those over 60 years of age. The values of the latter were similar to normal controls. There was little difference between the groups 24 hours later, however. Impaired absorption in the older age group was believed to account for the observed differences.

80. Myocardial Uptake of Free Fatty Acids in Dogs

L. J. Finkelstein, J. J. Spitzer and J. C. Scott. From The Hahnemann Medical College and Hospital, From the Institute of Cardiovascular Research and Department of Physiology, Philadelphia, Pa.

Coronary blood flow was determined under chloralose anesthesia, using the nitrous oxide desaturation method. Free fatty acids (FFA) were estimated simultaneously in arterial and coronary sinus blood. The average uptake of FFA based on 54 normal dogs was 14 μEq/min./100 g. of myocardium, arterial level 0.922 μEq/ml., arteriovenous difference 0.246 μEq/ml., and coronary flow 57.3 ml./100 g. of myocardium/min. Norepinephrine infusion increased the arterial level, A-V difference, flow and FFA uptake. The means of these parameters, except flow, decreased 16 minutes, but increased 43 minutes after insulin. Alloxan diabetes caused an elevation in arterial FFA level, no consistent change in A-V difference and FFA uptake. There appeared to be no change in the same diabetic animals 15 minutes after insulin.

It can be concluded that FFA uptake of the myocardium seems to depend on the arterial FFA level under normal conditions and also after the administration of norepinephrine or insulin. The myocardium resembles the liver in this respect. The same relationship seems to hold in our preliminary group of hypoxic dogs. Here a great increase of flow is accompanied by a constant arterial level, a decrease in the mean A-V difference and little change in uptake. However, under other pathological conditions, such as diabetes, this relationship between arterial level and uptake does not hold, in our as yet limited number of experiments.

81. Progress in Breed Susceptibility Study of Rabbits Fed Cholesterol

Elizabeth M. Gaman and De Witt H. Smith. From the Arteriosclerosis Laboratory, New Jersey Neuro-Psychiatric Institute, Princeton, New Jersey

This is a supplement to last year's report in Circulation on the initial studies then accomplished in attempts to find a rabbit strain that would show consistent cholesterolemia and aortic lipid deposit on a test administration of 1 per cent cholesterol for 4 weeks to weanling litters of various pure bred and hybrid rabbits. Previously we showed that Dutch and Californian rabbits were consistent in cholesterolemia and that the commonly used New Zealand were not, together with Flemish and Chinchilla. All pure bred strains then tested showed very inconsistent atheroma of the aorta. Dutch and Flemish were resistant to atheroma. Only in hybrids with Californians were acceptable and consistent atheroma levels found. We hereby add that English Spot showed inconsistent cholesterol levels and were resistant to atheroma. Checker Giants showed consistency in atheroma but moderate variation in cholesterolemia. One litter of pedigree New Zealand showed consistent atheroma. Champagne D'Argent showed consistent cholesterolemia. Results using the breeds already tested but from different sources in general support previous records. Further studies of California hybrids have tended to confirm earlier findings that these rabbits showed consistent atheroma of the aorta and acceptable cholesterol level. Contemplated is the possibility of producing a new rabbit breed that will be consistent in atheroma and hypercholesterolemia.

82. The Effects of Phentolamine (Regitine®) on Serum Free Fatty Acids in a Patient with a Pheochromocytomia and in Normal Subjects

Eliahu Gilon, Paul S. Roheim and Howard A. Eder. From the Albert Einstein College of Medicine, New York, New York.

Injection of epinephrine and norepinephrine has been shown to cause a marked increase in serum free fatty acid (FFA). (Dole, Gordon and Cherkes) When norepinephrine was infused continuously into dogs there was a sustained elevation in plasma FFA (Havel and Goldfien). It was, therefore, of interest to study a patient with a surgically proven pheochromocytoma. Fasting levels of serum FFA obtained during periods of hypertension were within the range of normal fasted subjects. The fasting levels fell following the administration of glucose to the same extent that occurred in normals. Serum lipid and lipoprotein concentrations were also within the normal range.

Five mg. of phentolamine were administered on 2 occasions intravenously and on 1 occasion intramuscularly; the systolic blood pressure decreased

as much as 90 mm. of Hg. within 1 minute after the intravenous administration. Serum FFA in both venous and arterial samples decreased significantly immediately and then rose to levels appreciably above the control values within 15 minutes. In 5 control subjects serum FFA concentrations were determined following the intravenous administration of 5 mg. of phentolamine. None showed a significant drop in serum FFA and in all the FFA concentrations increased markedly.

83. The Effect of Dietary Fat on Serum Total Cholesterol Concentration in the Dog

Francisco Grande, Donald S. Amatuzio and Sohachi Wada. From the Jay Phillips Research Laboratory of Mount Sinai Hospital, Minneapolis, Minnesota

Serum cholesterol responses to changes of dietary fat were studied in dogs by means of controlled feeding experiments of switchback design. The basic low fat diet (LFD) had 4 per cent of fat calories; the high fat diet (HFD) was prepared by mixing LFD with the experimental fats to make 40 per cent fat calories. Mean serum total cholesterol of 18 dogs was 135 mg./100 ml. (SEM 6.0) on LFD and 188 mg./100 ml. (SEM 7.5) when on a lard HFD, ($p < 0.0001$). Mean cholesterol of 10 dogs increased 29 mg./100 ml. ($p = 0.035$) when HFD of sunflower oil was compared with the LFD. Sixteen dogs had mean cholesterols of 198 mg./100 ml. (SEM 10.3) when on lard HFD, and 172 mg. when on sunflower oil HFD ($p = 0.003$). A HFD of linseed oil containing approximately 50 per cent of its fatty acids as linolenic acid was compared with another HFD containing a mixture of safflower, sunflower and coconut oils matching the linseed oil in the proportion of saturated, monoethenoid and polyethenoid fatty acids, and in which the polyethenoid fatty acids were mainly linoleic acid. Mean cholesterol of 8 dogs was 218 mg./100 ml. (SEM 30.9) on linseed oil HFD, and 228 mg. (SEM 29.5) on the HFD containing the mixture of oils ($p = 0.017$). Six dogs fed a HFD of linseed oil showed mean serum cholesterol 38 mg./100 ml. lower than when fed a HFD containing tung oil ($p = 0.05$).

84. Antihypercholesteremic Properties of a New Compound, Tris-(2-Dimethylaminoethyl) Phosphate Trihydrochloride (SKF No. 7732-A_3)

Samuel M. Greenberg, John F. Herndon, Edna C. Dick and T. H. Lin. From the Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania

In naturally hypercholesteremic dogs (total plasma cholesterols more than 150 mg. per cent), neither dimethylaminoethanol (40 mg./Kg./day) had any anticholesteremic effects. In these same dogs, dimethylaminoethanol as the tris ester of phosphoric acid (trihydrochloride), administered p.o., caused reductions in plasma total cholesterol of 30 per cent from pre-treatment levels during 13 weeks of treatment at a dosage of only 5 mg./Kg., b.i.d. Dogs with initial cholesterol levels over 215 mg. per cent maintained these reductions for 21 weeks (termination of experiment), while dogs with lower initial cholesterol levels gradually returned to their pre-treatment values during the final 6 weeks of treatment. Initial plasma cholesterol level seems to determine the effectiveness of the compound as an antihypercholesteremic agent. Plasma phospholipids were also lowered, whereas plasma total lipids remained essentially unchanged. The drug showed *in vivo* chylomicron clearing activity. Metabolic function tests during the final 2 months of treatment and histopathological examination upon autopsy revealed no abnormalities. The *in vivo* effects observed with this compound closely parallel *in vitro* results.

85. The Effect of Hyperlipemia on a Thrombic Index

J. Wilfred Hahn and Nicholas T. Werthessen. From the Southwest Foundation for Research and Education, San Antonio 7, Texas

The induction of the clotting process in blood requires a stimulus. It is reasonable to assume that given a fixed stimulus various bloods (or the same blood under different physiological conditions) would respond differently to that stimulus. In this study this variation of response of blood to a fixed stimulus has been called a "Thrombic Index." The index is based on the fact that 2 different stimuli produce not only different whole blood clotting times but also different prothrombin utilization values. By combining these observations in an appropriate formula based on physicochemical considerations it is possible to derive the Thrombic Index employed.

The possible role of lipemia in rendering the coagulation process more liable to occur *in vivo* has long been recognized. For these studies human subjects have been employed as well as baboons. It was found that marked differences in susceptibility could be observed in subjects after the ingestion of a fatty meal. The tendency of the subject's blood to form a thrombus as measured by the Index remains constant for 2 hours after ingestion of the meal. Then, concomitant with a continual increase in lipemia, the Index rises to as much as 2 times the control level.

The implications of these findings as regards the induction of thrombi based on atheromata will be discussed.

86. Atherosclerosis: Possible Role of Phagocytosis.

Denham Harman. From the Department of Biochemistry, University of Nebraska College of Medicine, Omaha, Nebraska

Injury to endothelial cells enhances their phagocytic activity. Since atherosclerosis tends to develop in areas of mechanical stress the possibility arises that lipid localization may be partly related to phagocytosis of lipoproteins by overlying endothelial cells. If so, lipoprotein surface properties may influence the rate of phagocytosis and hence the development of atherosclerosis.

The β-lipoprotein surface properties of 18 fasting human serums, as reflected by their paper strip electrophoretic mobility (EM), were studied before and after incubation at 37° C. (48 hours) under air and nitrogen and an additional 18 in this manner plus in the presence and absence of copper acetate (9.1 mg. per cent). Serum free fatty acids (FFA) were also determined.

Incubation in air increased EM from 1.8 - 3.7 cm. (aver. 2.7) to 1.9 - 4.8 (aver. 3.3); under nitrogen the corresponding figures were 1.6 - 3.4 (aver. 2.6) and 1.9 - 4.0 (aver. 3.2).

Copper acetate increased EM from 1.9 - 4.1 (aver. 2.8) to 3.2 - 5.7 (aver. 4.3) in air; under nitrogen from 1.9 - 3.7 (aver. 2.7) to 2.5 - 4.5 (aver 3.5).

FFA (μEq/L.) increased from 100-1000 (aver. 520) to 1400-3800 (aver. 2280) after incubation (independent of air, N_2, or copper); poor correlation between FFA and EM.

Incubation in air in presence and absence of copper (10 sera) had no effect on the low-density lipoprotein ultracentrifugal patterns.

Thus it seems likely that serum lipoprotein surface properties change *in vivo*, due, at least in part, to changes in FFA (ester hydrolysis, stress) and lipoprotein oxidation by O_2. Such changes may play a role in atherosclerosis by altering the rate of the postulated phagocytic activity of endothelial cells.

87. Influence of Medial Pathology on Atherogenesis in Dogs

A. C. Higginbotham and F. H. Higginbotham. From the School of Medicine, West Virginia University, Morgantown, West Virginia

Atherosclerotic lesions produced in dogs by suppressing the thyroid with thiouracil while feeding a cholesterol enriched diet appear to be similar to those in human beings in microscopic appearance and in distribution. However, before relying upon canine atherosclerosis as an experimental model for the human disease, a thorough comparative study of the factors involved in both is highly desirable.

In this study, a litter of mongrel beagles consisting of 1 male and 3 females was given thiouracil daily and fed a lipid enriched diet for 1 year. At sacrifice the aortas and coronary arteries were dissected out and studied grossly and microscopically for indications of arteriopathy. No coronary or aortic atherosclerosis was found in 2 of the females. The third female had extensive coronary lesions, but only 1 small aortic lesion in the abdominal segment, indicating a possible negation of estrogen protection of coronary arteries by thiouracil. The coronaries of the male were extensively involved and, in addition, there were fatty streaks and sizable plaques in the aorta, particularly around the orifices of its branches. Medial pathology was always associated with the intimal lesions, regardless of the size of the latter. The larger plaques always overlay areas of severe medial damage; smaller lesions were associated with a lesser degree of medial involvement. These observations suggest that, as in human beings, early medial pathology may play an important role in initiating the formation and extension of atherosclerotic lesions.

88. Effect of Male and Female Gonadal Hormones on Plasma Lipids and on Atherogenesis in the Rabbit

Peh-Ping Ho, Louis E. Schaefer and David Adlersberg. From the Mount Sinai Hospital, New York, N. Y.

In view of contradictory findings on the effect of gonadal hormones, particularly male hormones, on circulating lipids and on atherogenesis in the experimental animal, a systematic study was undertaken to determine these effects over a prolonged period of time in the rabbit.

One hundred forty-seven male rabbits were separated into several groups, and various treatment regimens and combinations employed. These involved castration, cholesterol feeding, testosterone injection, and use of estradiol for periods of time up to 4 months. Total and free cholesterol, serum phospholipids and serum total lipids were determined periodically. The animals were sacrificed at the conclusion of each experimental period and post-mortem studies were performed.

The role of the male gonads per se in regulating serum lipids and affecting atherogenesis appeared to be of minor importance under the experimental conditions which obtained. In contrast, the fe-

male gonads appeared to be of major importance in lowering circulating lipid values and in retarding atheroma formation. Estrogen protected the rabbits from hypercholesteremia and atherogenesis only for a certain critical period of time, however, and could be said to produce a "delaying" or "retarding" effect rather than a "preventive" or "protective" one.

These findings are in accord with the clinical facts relating to the differences between men and women in regard to serum lipid levels and incidence of coronary atherosclerosis. No clues as to the mechanisms by which estrogens exert their effects were gleaned from this study. The theory that they work through genetically-determined enzymatic reactions is an attractive one, requiring further elucidation.

89. The Effects of Triparanol on Body Cholesterol and Sterol Metabolism

William Hollander and Aram V. Chobanian. From the Evans Memorial Hospital, Boston, Mass.

The present study was undertaken because of reports that sterols other than cholesterol appear in the blood during triparanol therapy.

Our metabolic studies indicate that triparanol produces:

1. A highly significant and sustained reduction in serum cholesterol.
2. A significant decrease in the total sterols of the blood but to an extent less than the reduction of serum cholesterol.
3. A significant decrease in the "miscible pool" of cholesterol as determined by the disappearance curves of intravenously administered C^{14}-labeled cholesterol.
4. A significant decrease in the "total sterol pool" as indicated by serum specific activity of the total sterols as well as by dibromide purification of serum cholesterol.
5. A significant decrease in the amount of both cholesterol and total sterol that is turned over per day.
6. A significant reduction in the formation of radioactive sterol from administered C^{14}-labeled acetate or C^{14}-labeled mevalonic acid.

These metabolic changes caused by triparanol revert to control values after withdrawal of the compound.

Triparanol is effective in reducing both serum cholesterol and the "miscible pool" of cholesterol in man. The compound also reduces significantly the total sterol content of the blood as well as the "total sterol pool." These effects appear to result from an interference with the biosynthesis of cholesterol.

90. The Effect of Cigarette Smoking and Nicotine Administration on Serum Free Fatty Acids

Alfred Kershbaum, Samuel Bellet, Edward P. Dickstein, Leonard J. Feinberg and Paolo Rossi. From the Philadelphia General Hospital, Philadelphia, Pa.

The response of serum free fatty acids (FFA) to cigarette smoking was studied in 17 subjects. Two cigarettes were smoked in a 10-minute period and the serum FFA concentration was determined before and after smoking and at subsequent 10-minute intervals. In all subjects the FFA levels rose at the end of the smoking period, and the maximal elevation usually occurred 10 minutes later. Twenty and 40 minutes after smoking the FFA were still above the pre-smoking level in most instances. The maximal rise in FFA varied from 98 to 590 μEq./L., with a mean increment of 301 μEq./L. There was essentially no change in the serum total cholesterol and triglycerides in these experiments. In a control group who did no smoking there was an average increase in FFA of 4 μEq./L. over a 20-minute period. In order to simulate "chain-smoking" another group of 5 subjects smoked 6 cigarettes over a period of 40 minutes. All of these subjects showed a rise in FFA which was sustained throughout a total interval of 60 minutes. In animal studies nicotine was administered by continuous intravenous infusion at a rate of 20 gamma/Kilo/min. over a 20-minute period. In 13 of 15 observations there was a mean maximal elevation of FFA of 166 μEq./L. which usually occurred 10 minutes after the start of infusion. The observations made in these studies indicate that cigarette smoking and nicotine administration are followed by mobilization of FFA. These findings suggest the possibility that a repeated rise in FFA could be related to a disturbance in other serum lipids.

91. Frequency of Overweight, Obesity, Elevated Blood Pressure and Serum Cholesterol in Man Classed According to Physical Activity

Ancel Keys, Ratko Buzina, Flaminio Fidanza, A. del Vecchio, A. S. Dontas and Josef Brozek. From the Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn.

In 4 rural areas 96 to 99 per cent of all men aged 40-60 or 45-60 were examined (2597 men). For each area and age-quinquennium group decile values were determined for relative body weight, obesity (skinfold thickness), systolic and diastolic blood pressure and serum cholesterol. In each of these groups the men classed as sedentary or light

physical activity contributed an undue proportion o the upper end of the distribution for each of hese variables. The average *excess* representation bove the 80th centile of the sedentary-light activ- ty class was 65 per cent for relative weight, 80 er cent for obesity, 22 per cent for systolic blood ressure, 45 per cent for diastolic blood pressure, nd 25 per cent for serum cholesterol. For men of he same age there were no important differences etween the areas in relative weight, obesity or lood pressure but there were significant differ- nces in serum cholesterol. The implications for he epidemiology of heart disease will be discussed.

92. Cyclical Re-Utilization of Cholesterol in Atherosclerotic Lesions

Abel Lazzarini, Jr., and Jere W. Lord, Jr. From the New York University Medical Center, New York, N. Y.

Endothelial cells obtained from the intima of short-term organ cultures of the aorta and coronary vessels of patients with severe atherosclerosis were maintained in media containing aqueous microemulsions of C^{14}-cholesterol. After incubation, the cells were rinsed in a balanced salt solution and transferred to a cholesterol-free medium.

It was observed that those cells which had high concentrations of intracellular cholesterol did not return to their initial state but degenerated and their protein-bound cholesterol was immediately incorporated by surrounding cells of the same type. This cyclical re-utilization would then continue until all endothelial cells were destroyed unless it was inhibited by the addition of heparin or unsaturated acids to the medium.

These results suggest that cholesterol re-utilization may play a role in atherosclerosis and could explain the clinical findings of atherosclerotic patients with normal cholesterolemia since atherogenesis could continue independent of blood cholesterol levels once the initial arterial lesion had been produced.

93. Estrogen Effect on Survival in Men Who Have Suffered a Myocardial Infarction: An Interim Report

Jessie Marmorston, Frederick J. Moore and Oliver Kuzma. From the University of Southern California School of Medicine, the Los Angeles County Hospital and the Cedars of Lebanon Hosptial, Los Angeles, Calif.

A total of 338 men, aged 36 to 87, have entered he study: 250 were alive in project 12 months, 46 for 2 years, 71 for 3 years. On entry patients ere randomly allocated to ethinyl estradiol, ethoxy-methyl-estriene-diol, mixed conjugated equine estrogens, or placebo. Low initial estrogen dosage was increased gradually to the point of minimal breast changes and continued at tolerated levels. Representative doses were 0.1 mg. ethinyl estradiol, 10 mg. methoxy-methyl-estriene-diol, and 2.5 mg. conjugated equine estrogens daily. Ethinyl estradiol and methoxy-methyl-estriene-diol were found to lower cholesterol, the C/P ratio, and per cent of beta-lipoproteins and to raise phospholipids.

In the series as a whole, survival rates were higher in estrogen-treated men than in the controls, this difference attaining statistical significance in early time periods where rather large numbers of subjects have been studied.

94. Metaplasia in the Aortic Wall Following Intramural Carrageenan

Esther L. McCandless and Judith M. Lehoczky. From the University of Buffalo Chronic Disease Research Institute, Buffalo 14, N. Y.

Subcutaneous injection of carrageenan is known to stimulate growth of fibroblasts and production of collagenous connective tissue. To study the tissue produced in the arterial wall, 1 per cent carrageenan in saline was injected into the aortic arch of cockerels. Control chickens received 5 per cent gelatin injections. The injection site was marked by thread placed in the adventitia. Animals were sacrificed 3 to 12 weeks after injection.

When carrageenan was injected into the media or intima, the tissue produced was characterized by large rounded cells imbedded in a homogenous matrix which stained metachromatically with toluidine blue, faintly positive with PAS, and blue with Heidenhain's azan. The area strongly resembled developing cartilage. Immediately adjoining this area, muscle cells showed metaplastic change; horizontal nuclei of muscle bundles assumed a palisaded position and appeared to be incorporated in the newly developing cartilage. Injections into the adventitia were marked by extensive collagen development as in subcutaneous injections. The differences in characteristics of connective tissue produced in intima and adventitia suggest that the modifications in vascular structure are a response to physical forces and environmental factors. These findings support previous suggestions that the force of the pulse wave may contribute to arterial structure.

95. Role of Dietary Protein on the Development of Ulceration in Atherosclerotic Lesions in Cockerels

Ruth Pick, Louis N. Katz and Philip Johnson. From the Cardiovascular Department, Medical Research Institute, The Michael Reese Hospital and Medical Center, Chicago, Ill.

Ulcerated coronary and abdominal aorta lesions have been produced by estrogens in atheromata induced by low-protein atherogenic diet.

Two further experiments are now reported. In one, birds were fed the low-protein atherogenic diet for 7 weeks, then during the next 5 weeks were separated into 4 groups. Groups 1 and 2 were continued on the previous diet. Groups 3 and 4 were switched to a low-protein regular mash diet. Estrogens were added to Groups 2 and 4. Birds were sacrificed weekly.

Both estrogen groups developed ulcerated abdominal aorta lesions, most frequently after 3-4 weeks of treatment. In the 5th week, ulceration also occurred in the abdominal and thoracic aorta in Groups 3 and 4.

The second experiment was like the first in the first 7 weeks. In the 8th to 10th weeks, with the atherogenic diet continued and estrogen simultaneously exhibited, birds were separated into a low-protein (10 and 15 per cent) and a high-protein (20 and 36 per cent) group. Abdominal aorta ulcerations were similar in both groups after 2 weeks (12 of 31 versus 14 of 38 birds), but a striking difference occurred after 3 weeks—19 of 36 birds (53 per cent) in the low-protein versus 6 of 29 birds (21 per cent) in the high-protein group.

Dietary protein, thus, plays a definite role in the development of atherosclerotic ulceration. Preliminary histological observations suggest a difference in fibroblastic activity of atheromata produced with different dietary protein levels.

96. Influence of Dietary Fat on Cholesterolemia in Normal, Hyperthyroid and Hypothyroid Rats

Karoly G. Pinter, James G. Hamilton and O. Neal Miller. From the Department of Biochemistry and Nutrition and Metabolism Research Laboratory, Department of Medicine, Tulane Medical School, New Orleans, La.

Six groups of rats (10) were maintained on diets in which 40 per cent of the total calories were supplied by butter (groups A, B, C) or cottonseed oil (groups D, E, F). Diets 1 and 4 were supplemented with 0.3 per cent of thiouracil and diets 2 and 5 supplemented with 0.05 per cent iodinated casein and were designated as "hypo-" and "hypermetabolic" diets respectively. Control diets (3, 6) contained neither thiouracil nor iodinated casein. At the end of each experimental period, 2 weeks, each group of animals was changed to one of the other diets, i.e., groups A, B and C were fed either diet 1, 2 or 3 and groups D, E and F were fed either diet 4, 5 or 6. Plasma cholesterol levels were determined weekly by quantitative glass paper chromatography. Results were expressed as mg. per cent and as per cent changed from control value. Representative data which resulted from these changes in diet are as follows: 1) from laboratory chow to hypermetabolic diets (2 and 5); 74 to 99 (34 per cent increase) and 73 to 82 (only 12 per cent increase) respectively, 2) from "chow" to "hypometabolic" diets (1 and 4); 79 to 246 (211 per cent increase) 92 to 200 (only 117 per cent increase) respectively; 3) from "hypometabolic" to "hypermetabolic" diet (1 to 2 and 4 to 5) 206 to 157 (24 per cent decrease); 192 to 119 (38 per cent decrease) respectively; 4) from "hypermetabolic" to "hypometabolic" diet (2 to 1 and 5 to 4) 104 to 129 (24 per cent increase); 126 to 79 (35 per cent decrease) respectively. The data indicate that unsaturated fat has a cholesterol lowering effect which is independent of the state of thyroid function.

97. Free Amino Acids and Other Constituents of Blood and Aorta of Rabbits with Normo- and with Hyperlipemia-Cholesterolemia

O. J. Pollak and Araceli F. Engel. From the Dover Medical Research Center, Inc., Dover, Del.

Free amino acids, total protein, lipid and cholesterol were assayed in blood serum and in tissue extracts of ascending, thoracic and abdominal aorta of healthy rabbits and of rabbits with induced hyperlipemia and hypercholesterolemia.

The aminogram of tissue extracts did not reflect that of serum in either series. Amino acid patterns of the same aortic sector differed from one rabbit to another and the composition of 3 aortic sectors from one and the same rabbit varied, too. There were marked differences between amino acids of normal and diseased animals. Glutamic acid, lysine and isoleucine were far more often found in aorta of hyperlipemic than of normolipemic rabbits. While isoleucine was never present in blood serum, glutamic acid and lysine were found in normal but not in abnormal serum. Cysteine was not detected but norleucine was increased in diseased ascending aorta. The frequency with which free amino acids were recovered in diseased animals increased for serum by 40, in the ascending aorta by 83.5, in the thoracic aorta by 72, and in the abdonimal aorta by 20.5 per cent.

Feeding of eggs fried with butter resulted in 15-fold increase of total cholesterol 5-fold increase of total lipid and 3/5 increase of total serum protein. Cholesterol in the ascending aorta increased 7-fold, in the thoracic aorta 3-fold. Lipid increased 3-fold in the ascending and thoracic aorta. Total protein increased 2½-fold in the ascending and 2-fold in the thoracic aorta. No increases were detected in the abdominal aorta.

98. Normal Rabbits' Aortic and Myocardial Cells Cultured in Various Media

O. J. Pollak and Tatsuo Kokubu. From the Dover Medical Research Center, Inc., Dover, Delaware.

Samples of the inner layers of ascending, thoracic and abdominal aorta and of myocardium of healthy rabbits were planted on Eagle's basal media supplemented by 14.6 mg. of glutamine and 15 ml. of chicken embryo extract, either without serum additive or enriched by the addition of 15 ml. of rabbit, horse, human or chicken serum per 100 ml. of media.

The largest number of positive cultures and the most abundant growth were obtained in media containing rabbit serum. Horse serum and human serum were comparable; chicken serum was least suited. Myocardial cells grew best even in media without serum. Growth of thoracic aortic cells was less abundant, those of abdominal origin least, ascending aorta cells grew best. This pattern was also true for the earliest appearance of cells *in vitro*. Earliest growth was seen 48 hours after inoculation. Usually, it took 5 days for primary growth to develop, sometimes 8 days.

Qualitative differences were not striking except for chicken serum which caused increase in size of aortic cells and appearance of cytoplasmic granules and, in later stages, also changes in the shape of cells.

Differences in the number of positive cultures, in earliest appearance of cells *in vitro*, in cell multiplication (growth curve) and in the morphologic character of cells are ascribed to differences in the biochemical environment. Blood serum of several species has not the same composition and neither does the serum of animals of the same species, especially with regard to the qualitative and quantitative amino acid spectrum.

99. Effect on Serum Cholesterol of a Prudent-Type Reducing Diet: Study of 111 Obese Men 50-59 Years of Age

Seymour H. Rinzler, Morton Archer and Norman Jolliffe. From the Diet and Coronary Heart Disease Study Project, Bureau of Nutrition, New York City Department of Health, New York, N. Y.

In the 50-59 year age group, 207 obese men were placed on a prudent-type reducing diet: calories about 1600, protein 140 Gm., carbohydrate 180 Gm. and fat 33.5 Gm. (19 per cent of total calories) with saturated, monounsaturated and polyunsaturated fatty acids supplying 7.8, 6.5 and 4.7 per cent of total calories respectively. The addition to this diet of 1½ oz. of corn oil daily plus more fruits and vegetables if required converts it to the prudent diet previously described.

Of this starting group, 111 adhered so rigidly to the prescribed diet as to achieve a Performance Index of 85 or better during the first 10 weeks of observation. Their average control serum cholesterol dropped from 261 to 225 mg. per cent by the end of 6 weeks and remained level thereafter. Of the 111 men, 97 reduced to desirable levels, 74 of these have been maintained on the prudent maintenance diet for at least 6 months, and 56 of these maintained for 1 year with the average serum cholesterol remaining level.

The average cholesterol of the top, middle and low thirds fell from 307, 251 and 207 mg. per cent, respectively, to 254, 222 and 189 mg. per cent, respectively. Maintenance of weight (after successful weight reduction) by use of the prudent maintenance diet serves to maintain the lowered cholesterol level and prevents its rebound. The lower limit reached by each tertile corresponds very closely to its counterpart in the normal weight men with the major point of difference being the earlier fall achieved on the reducing diet.

100. Atherosclerotic Lesions Produced in Dogs by Prolonged Administration of Triton WR-1339

Angelo Scanu, Pasquale Oriente, Janus M. Szajewski and Irvine H. Page. From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

Studies were performed to test the hypothesis, suggested by *in vitro* experiments, that a primary physico-chemical alteration of plasma lipoproteins is responsible for the hyperlipemia which develops in animals following Triton administration. Male dogs on a regular diet received intravenously 250 mg./Kg. of Triton every 4th day. The clinical course could be divided into 3 stages. In 1 of 1-2 week duration plasma lipoproteins remained normal. In stage 2 of 1-2 month duration all lipid classes including free fatty acids rose progressively. The development of the hyperlipemia was accompanied by reduction, followed by total disappearance of plasma α-lipoproteins (d 1.063-1.21). When greater lipemia developed (up to 20 gr. per cent of total lipids) most of the β-lipoproteins floating at d 1.063 were also absent from plasma, the lipids being floated at lower densities. In stage 3 or terminal of 1-3 week duration the hyperlipemia animals showed weight loss and trophic lesions of the skin followed by death. Autopsy revealed marked atherosclerotic lesions of the coronary vessels accompanied in 2 dogs by clear evidence of myocardial infarction. In the

aorta presence of fatty streaks was made evident by Sudan IV. Microscopic findings were consistent with genuine atherosclerosis. Some of the dogs while receiving Triton were injected daily with heparin (5 mg./Kg./day). The course of the disease was not significantly changed. Experiments with I^{131}-lipoproteins, injected into dogs in the hyperlipemic phase, indicate that splitting of lipoproteins had occurred due to lipid displacement by Triton.

101. Change of Serum Lipid Levels with Age: A Five-Year Longitudinal Study

Louis E. Schaefer, Arthur G. Steinberg, David Aldersberg and Gilberto Ramirez. From the Mount Sinai Hospital, New York, N. Y.

This investigation involves the re-examination of an ambulatory population 5 years after the first study. Twelve hundred persons in Staten Island, N. Y., from 2-72 years of age, were originally investigated and average lipid levels computed for 5-year age groups. All available participants in that study are being systematically recalled, and, to date, approximately ½ have been re-examined. It has thus been possible to calculate the actual change with age, for several different age groups, over a 5-year period.

The actual change with time was always in the same direction, and of approximately the same magnitude for all ages in both sexes as the change predicted from the original study. Confirmation of the following predicted trends in serum cholesterol level was obtained: in the female, pre-adolescent decrease followed by an equivalent post-adolescent increase; relative constancy from post-adolescence to the mid-30's; marked increase after age 35. In the male, pre- and post-adolescent fall and rise of considerably less magnitude than in the female; sharp increase from age 20-40; relative constancy after age 40.

The average change of a group was not participated in by all individuals in the group. For example, the average change of 40 pre-adolescent females was from 210 mg. at age 8 to 193 mg. at age 13, but 11 of the 40 increased rather than decreased. Approximately 35 per cent of individuals in each age group moved in a direction opposite the general trend. Usually, this opposite movement occurred in persons with low levels if the subsequent change for the group was downward, and in individuals with high levels if the subsequent group change was upward.

It is possible that the age-change pattern of cholesteremia of an individual will provide a more accurate reflection of the presence or absence of abnormal lipid metabolism, than the evaluation of a single lipid value at a given point in time.

102. Relation of Water Hardness and Death Rates from Cardiovascular Diseases

Henry A. Schroeder. From the Brattleboro Retreat, Brattleboro, Vermont and Department of Physiology, Dartmouth Medical School, Hanover, N. H.

Analyses by state of weighted average water hardness (1950-51) and death rates (1949-51) from the 10 leading causes of death in the total population showed high-negative correlation coefficients with cardiovascular diseases and vascular lesions affecting central nervous system ($p < 0.01$), and high-positive coefficients with motor vehicle accidents and congenital malformations. When confined to white persons aged 55-64 and divided into specific diseases, high-negative correlations appeared for hypertension ($p < 0.01$), arteriosclerotic heart disease ($p < 0.01$), general arteriosclerosis ($p < 0.02$), and vascular lesions affecting central nervous system ($p < 0.02$). Coefficients were small for rheumatic, endocarditic, nephritic and other diseases of heart. A high-negative correlation appeared for one neoplasm, that of male respiratory tract, and a high-positive one for congenital malformations at all ages. Coefficient was possibly significant ($p < 0.05$) for cirrhosis of liver. Others were small: diabetes mellitus, pneumonia, peptic ulcer, senility, hernia and 5 neoplasms. Correlation of motor vehicle accidents with water hardness appeared mainly on geographical basis. The existence of coefficients of statistical significance with water hardness and all major disorders secondary to hypertension and atherosclerosis suggest either a causal relationship or one in which each of these factors is related to a third.

103. Effect on Serum Lipid Levels of Corn Oil Versus Pure Oleic and Linoleic Acids in "Atherogenic-Thrombogenic" Diets for Rats

Robert F. Scott, Margaret M. deMaine and Wilbur A. Thomas. From Albany Medical College, Albany, N. Y.

Various diets inducing "atherosclerosis" and thrombosis in rats have been described. These atherogenic-thrombogenic diets utilize, among other ingredients such as cholesterol and propylthiouracil, different naturally occurring fats and result in high serum lipids. In the current experiment certain pure fatty acids were substituted for natural fat in one of these diets in an attempt to identify specific dietary fatty acids influencing serum lipids.

For 10 per cent corn oil in one type of atherogenic-thrombogenic diet, 10 per cent oleic acid was substituted. In another experiment, a 7.5 per cent linoleic/2.5 per cent oleic acid mixture replaced 10 per cent corn oil. Serum cholesterols, lipid phosphorous and triglycerides were measured in 50 rats.

When 7.5 per cent linoleic/2.5 per cent oleic acid replaced corn oil in the diet, serum lipid levels fell between the "corn oil" group and the "oleic" group. Mean values for "corn oil," "linoleic/oleic" and "oleic" groups were respectively: cholesterol: (expressed as mg. per cent) 1234, 1668 and 2530; lipid phosphorus (as micromols per ml.) 6.39, 8.37 and 14.19; triglycerides: (as mg. per cent triolein) 476, 531 and 991.

It is perhaps to be expected that substitution of pure oleic for corn oil would result in higher serum lipid levels but surprising that increased concentrations of linoleic failed to result in lower levels.

104. Antithrombolic Effects of a Monoamine Oxidase Inhibitor

Takio Shimamoto. From the Tokyo Medical and Dental University, Tokyo, Japan

Recently we found that a small amount (0.1 — 1.0 μg./Kg.) of adrenaline produces damages to the "silicone-like property" of blood vessels of rabbits (and men), inducing an abrupt swelling of endothelial cells, appearance of stickiness of these cells to platelets and leukocytes, formation of white thrombi and at the same time an abrupt decrease in platelet count as well as an abrupt shortening in blood coagulation time. On the other hand noradrenaline was found to be practically ineffective.

Such phenomena were also shown to be produced by oral administration of cholesterol or some fatty substances or by intravenous injection of bacterial polysaccharide.

A monoamine oxidase inhibitor was found to prevent such phenomena induced by adrenaline cholesterol or pyrogenic substances.

In the long-term regimen on rabbits the administration of 10 mg. of this monoamine oxidase inhibitor daily was found to prevent the appearance of atherosclerosis by cholesterol feeding.

Using Sandison-Clark's technique modified by Ebert, we took a motion picture of above-mentioned effect of cholesterol, adrenaline and bacterial polysaccharide in inducing the swelling of endothelial cells of blood vessels, appearance of stickiness of these cells to platelets and leukocytes, and the appearance of white thrombi.

105. Effect of Vegetable versus Animal Fat on Rat Serum Lipfanogens

Henry S. Simms. From Columbia University, College of Physicians and Surgeons, New York, N. Y.

The fat-depositing action of rat serum (as measured by the free-lipfanogen levels) was higher on a diet containing vegetable oil (Mazola) than on a diet containing animal fat (lard). The former had 5.0 units of free lipfanogens, while the latter had 3.5 units. The p value was < 0.05.

The free antilipfanogen (which serves to reduce fat deposition) was correspondingly lower in the serum of Mazola-fed rats (30.5 units) than for the lard-fed rats (37.6 units)—but the differences were less significant ($0.1 < p < 0.2$).

Data on the effect of long-chain and medium-chain triglycerides were also obtained, as well as data on the lipfanogen and antilipfanogen levels in the serum of rats without added fat.

106. Organ Susceptibility in the Rabbit to Cholesterol Feeding

DeWitt H. Smith and Elizabeth M. Gaman. From the New Jersey Neuro-Psychiatric Institute, Princeton, N. J.

Largely based on studies in breed susceptibility in which weanling litters of various rabbit breeds and hybrids have been fed 1 per cent cholesterol for a 4-week period prior to sacrifice but supplemented by some long-term experiments, we have found variations in the susceptibility of the arterial wall of different organs to lipid deposits. The organs most affected are the spleen, aorta and heart. Fewer lesions are found in the kidney, liver and meninges. In the spleen, there is a maximal involvement of the smaller arteries in the germinal centers. Essentially no lesions are found in the gonads, thymus and other organs which are not routinely inspected. In the aorta, characteristic maximal involvement is found in the areas around the openings of the great vessels from the aortic arch, with "V" shaped lesions seen at the openings of the intercostal and large abdominal vessels. Variable other lesions are found throughout the remaining portions of the aorta. In heavily affected rabbits, there is involvement of the common carotids and large abdominal arteries. Coronary vessels may show intimal proliferation if heavily involved. That the rabbit aorta is most involved in the aortic arch is different from the human. The manner in which the vessels are held fixed in the thorax may be a factor, as well as that the aortic arch is more dependent in the rabbit than in the human.

107. Sex and Race Differences in Coronary Atherosclerotic Lesions

Jack P. Strong and Henry C. McGill. From the Louisiana State University School of Medicine, Department of Pathology, New Orleans, La.

Atherosclerotic coronary artery lesions were graded in 182 white males, 65 white females, 188 Negro males and 113 Negro females from 1 to 69 years of age according to percentage of intimal surface involvement with fatty streaks, fibrous plaques, complicated lesions (hemorrhage, ulceration or thrombosis) and calcified lesions. The earliest grossly detectable lesions are fatty streaks which first appear in all groups from 10 to 19 years of age. White males have more fatty streaks than any other group up to age 39 with one exception (Negro females 20-39 years of age). Fibrous plaques appear in white males in the 20-29 year group but not in other groups to a significant degree until the 30's. White males have more fibrous plaques than white females at all ages, the difference being the greatest in the 30-39 year group. The male-female difference in fibrous plaques is variable in the Negro. Complicated lesions and calcified lesions appear first in the white males (30-39 years) and are more extensive than in the other groups at all subsequent ages. The differences in coronary lesions are similar in direction and magnitude to widely recognized sex-race differences in incidence of clinical coronary disease. Development of fibrous plaques from fatty streaks appears to be the critical phase in the natural history of atherosclerosis which correlates most closely with clinical disease.

108. Influence of Pseudopregnancy, Prolactin and Progesterone on Plasma Cholesterol Concentrations in Dogs

David M. Tennent and Mary E. Zanetti. From the Merck Institute for Therapeutic Research, Rahway, N. J.

Female beagles in this laboratory, fed a meat and meal diet, uniformly exhibit increased plasma cholesterol concentrations following sexual heat, even when they have not been mated. This cholesterol rise lasts for about 2 months, and the levels reached are about twice pre-estrus values. Similar cholesterol rises are produced by daily injection of progesterone or of prolactin, not only in intact females, but also in ovariectomized females and in normal males. The cholesterol rise is reversed in females by nicotinic acid feeding, but not by nicotinamide. It is also reversed by feeding the bile acid adsorbent, Cholestryramine Resin (MK-135), and the hepatic cholesterol synthesis inhibitor, benzmalecene.

109. Studies of Clot-Lysis in Rats with Particular Reference to "Atherogenic-Thrombogenic" Diets

Wilbur A. Thomas, R. Foster Scott and Khal Alousi. From the Department of Pathology, Albany Medical College, Albany, N. Y.

"Atherogenic" diets for animals were develope more than 50 years ago and subsequently innumerable experiments have been carried out in a effort to understand their mechanism of actio More recently modifications of "atherogenic" diet have been devised that are in addition "thrombo genic" (Thomas and Hartroft; Circulation 19:65 1959), and we are attempting to elucidate th chemico-pathologic pathways involved with thes diets.

Currently one aspect being explored is effect o "atherogenic-thrombogenic" diets on clot-lysis i rats. We developed methods (Tillman, Thomas, O'Neal; Circulation 20:989, 1959) by means o which we demonstrated that clot-lysis was prolonged in rats fed butter-containing, "atherogenic-thrombogenic" diets as compared with rats fed "normal" diets.

Since the last report, our studies of clot-lysis have been extended in 3 areas: 1) Previous results have been confirmed in 2 additional experiments involving 86 rats (43 pairs) with clots from rats fed "atherogenic-thrombogenic" diets resisting lysis significantly longer in 41 of the 43 pairs (mean lysis-times also significantly different). 2) An experiment has been performed involving 46 rats in which plasmas were stored in liquid nitrogen at −171 C for a period of several days and differences between animals fed different diets could still be readily demonstrated, thus opening the way for development of methods for long-term comparative studies in man or animals. 3) Experiments with 50 rats directed toward elucidating basic mechanisms have been carried out in which it has been shown that platelet solutions inhibit clot-lysis in the rat.

110. Serum Cholesterol, Lipid Phosphorus and Atherosclerosis in Chickens: The Effect of Diet, Age, Sex and Sex Hormones

Alice Trocchi and Donald L. Anderson. From the Poultry Science Department, University of Massachusetts, Amherst, Mass.

The relation of specific serum lipids to atherosclerosis was studied in chicks maintained in a replicated experiment for 4, 8, 12 and 16 weeks of age on various nonatherogenic regimens which employed dietary fat and sex hormone administration. By variance analysis significantly higher serum

cholesterol was observed in birds fed the more saturated fat diet (tallow) as compared to birds on the more unsaturated fat (corn oil) and control diets. Males had a significantly higher serum cholesterol and atherosclerotic score than females. Diethylstilbesterol in sesame oil, administered at 100 μg/100 Gm. body weight every 3.5 days, significantly elevated serum cholesterol, lowered serum cholesterol/lipid phosphorus (C/P) ratio and increased abdominal atherosclerosis. Testosterone proprionate at a dose of 20 μg/100 Gm. body weight every 3.5 days showed no consistent effect.

Spontaneous abdominal atherosclerotic lesions, observed in birds as early as 8 weeks of age, were augmented by high-fat diets and increased in severity as the birds matured.

It is concluded that high (C/P) ratios do not necessarily predispose atherogenesis. Failure to get a consistent correlation between serum cholesterol and atherosclerosis among the various treatments would suggest that a mechanism other than or in addition to hypercholesterolemia is involved in the production of the pathology. Local and hormonal factors are implicated.

111. Mast Cell Alterations in the Myocardium of Atherosclerotic Rats

Bernard C. Wexler, Thomas E. Brown and Benjamin F. Miller. From the May Institute for Medical Research, Cincinnati, Ohio.

It has been suggested that connective tissue mast cells may be related to the development of atherosclerosis because patients with this disease show a smaller number of mast cells than normals. In addition, the atherosclerosis-resistant rat possesses a high number of mast cells in the myocardium while the more susceptible rabbit and chicken contain a low number. Repeated breeding without rest between litters will produce atherosclerosis in the rat. The authors have found that unilateral nephrectomy and injection of ACTH intensify and increase the incidence of arteriosclerosis. Animals selectively bred and sacrificed after successive breedings demonstrate progressive accumulation of acid mucopolysaccharides and subintimal fibrosis. Continued breeding, and injection of ACTH coupled with uninephrectomy, cause greater pooling of mucopolysaccharides and fibrosis along with accelerated arteriosclerosis. Myocardial tissue from male and female breeder rats was stained with toluidine blue and studied in conjunction with the progressive development of the atherosclerosis. As the atherosclerosis became more pronounced the population of the myocardial mast cells decreased. ACTH and uninephrectomy aggravated the atherosclerosis and caused the greatest decrease in myocardial mast cells; the reaction of mast cell granules was changed from metachromatic to orthochromatic, indicating the likelihood of active secretion without cellular lysis. It appears that mast cell granule discharge is influenced by secretory activity of the adrenal glands. Also, it seems possible that the discharge and disappearance of myocardial mast cells may contribute to the accumulation of mucopolysaccharides in the experimental arterial lesions.

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PART ONE

CONTENTS

Editorial:

Opinions, Decisions, and Facts. Ancel Keys 501

Original Articles:

The Evolution of Rheumatic Heart Disease in Children. Five-Year Report of a Cooperative Clinical Trial of ACTH, Cortisone, and Aspirin. (United Kingdom and United States Joint Report) 503

Catecholamines in the Localization of Pheochromocytoma. J. Richard Crout and Albert Sjoerdsma 516

Heart Block after Repair of Ventricular Septal Defect in Children. Ronald M. Lauer, Patrick A. Ongley, James W. DuShane, and John W. Kirklin 526

Vasoconstriction and Medial Hypertrophy in Pulmonary Hypertension. C. A. Wagenvoort 535

Dynamic Aspects of Cholesterol Metabolism in Different Areas of the Aorta and Other Tissues in Man and Their Relationship to Atherosclerosis. Henry Field, Jr., Leon Swell, P. E. Schools, Jr., and C. R. Treadwell 547

Hemodynamics of Mitral Stenosis with Special Reference to Coronary Blood Flow and Myocardial Oxygen Consumption. George G. Rowe, George M. Maxwell, Cesar A. Castillo, John H. Huston, and Charles W. Crumpton 559

Central Circulatory Changes Accompanying Mitral Commissurotomy. Harold G. Richman, J. Bradley Long, and Elliot Rapaport 563

Renal Hemodynamic Responses to Stress in Normotensive and Hypertensive Subjects. C. T. Bello, R. W. Sevy, E. A. Ohler, C. A. Papacostas, and R. M. Bucher 573

Response to Exercise in Congenital Complete Atrioventricular Block. Danae Ikkos and John S. Hanson 583

The Direction of Blood Flow in Anomalous Left Coronary Artery Arising from the Pulmonary Artery. David C. Sabiston, Jr., Catherine A. Neill, and Helen B. Taussig 591

Sex Differences in the Electrocardiogram. Ernst Simonson, Henry Blackburn, Jr., Thomas C. Puchner, Pauline Eisenberg, Fernanda Ribeiro, and Manuel Meja 598

Studies of Peripheral Circulation during Sickle-Cell Crisis. Felice Manfredi, Angelo P. Spoto, Herbert A. Saltzman, and Herbert O. Sieker 602

Symposium on Coronary Heart Disease: *(To Be Continued)*

The Use of Anticoagulants in Coronary Heart Disease. Progress and Problems: 1960. Irving S. Wright 608

Thrombolytic (Fibrinolytic) Therapy for Coronary Heart Disease. Anthony P. Fletcher and Sol Sherry 619

Legal Aspects of Coronary Disease. Howard B. Sprague 627

Clinical Progress:

Atrial Repolarization—Its Importance in Clinical Electrocardiography. Joao Tranchesi, Victor Adelardi, and Jorge Martins de Oliveira 635

Abstracts 645

News from the American Heart Association 648

The Council on Arteriosclerosis of the American Heart Association, The American Society for the Study of Arteriosclerosis: Program and Proceedings of the Fourteenth Annual Meeting 650

Contributors to This Issue 690

PART TWO

Program and Abstracts, 33rd Scientific Sessions of the American Heart Association 693

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OCTOBER 1960
VOL. XXII NO. 4
PART TWO

Circulation

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PROGRAM and ABSTRACTS of AHA SCIENTIFIC SESSIONS

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ANNUAL MEETING—1960

All Sessions are held at Kiel Auditorium

SCIENTIFIC SESSIONS

		Friday, October 21	Saturday, October 22	Sunday, October 23
MORNING	SESSIONS ON CLINICAL CARDIOLOGY	Einthoven Commemoration CONNER MEMORIAL LECTURE: PHYSIOLOGY OF THE CIRCULATION AS VIEWED BY THE INTERNIST Jointly with American College of Cardiology SYMPOSIUM: ATRIAL ARRHYTHMIAS	Jointly with Council on High Blood Pressure Research SYMPOSIUM: DIAGNOSIS AND TREATMENT OF CURABLE HYPERTENSION Original Papers	Jointly with Council on Cardiovascular Surgery SYMPOSIUM: COMPLETE HEART BLOCK PANEL: SURGERY FOR EXTRACRANIAL OCCLUSIVE CEREBROVASCULAR DISEASE Original Papers
	SPECIAL AND COUNCIL SESSIONS	Council on Arteriosclerosis (I) Original Papers Council on Rheumatic Fever and Congenital Heart Disease Original Papers	Biophysical Methods in the Study of the Circulation Original Papers Council on Cardiovascular Surgery (I) Original Papers Council on Community Service and Education Session for Nurses (A.M.)	Council on Basic Science (I) SYMPOSIUM: PHYSIOLOGIC BASIS OF PULMONARY FUNCTION TESTS Original Papers Council on Community Service and Education SYMPOSIUM: NONDIETARY FACTORS IN CORONARY ARTERY DISEASE Original Papers Cardiovascular Films (I)
AFTERNOON	SESSIONS ON CLINICAL CARDIOLOGY	Jointly with Council on Rheumatic Fever and Congenital Heart Disease PANEL: CURRENT THERAPY FOR RHEUMATIC FEVER Original Papers	Jointly with Council on Circulation BROWN MEMORIAL LECTURE: CLINICAL PHYSIOLOGY OF THE SPLANCHNIC CIRCULATION Original Papers	Jointly with Council on Community Service and Education SYMPOSIUM: LIPIDS AND ARTERIOSCLEROSIS Original Papers
	SPECIAL AND COUNCIL SESSIONS	Council on Circulation Original Papers Council on Arteriosclerosis (II) Original Papers Council on Community Service and Education Medical-Dental Session	Council on Cardiovascular Surgery Jointly with Council on Rheumatic Fever and Congenital Heart Disease SYMPOSIUM: VENTRICULAR SEPTAL DEFECTS Original Papers Council on High Blood Pressure Research Original Papers Council on Community Service and Education Session for Nurses (P.M.)	Council on Basic Science (II) Original Papers Council on Cardiovascular Surgery (II) Original Papers SYMPOSIUM: HYPOTHERMIA AND EXTRACORPOREAL CIRCULATION Cardiovascular Films (II)
EVE		Jointly with American College of Cardiology "Fireside Conferences"	Council on Community Service and Education SEMINAR ON NUTRITION	

BUSINESS MEETINGS, LUNCHEONS AND DINNERS

Friday, October 21

Council on Clinical Cardiology
Business Meeting
Kiel Auditorium, Opera House
10:00 A.M.

Council on Rheumatic Fever and Congenital Heart Disease
Luncheon and Business Meeting
Kiel Auditorium, Assembly Hall 4
12:30 P.M.

Council on Circulation
Business Meeting
Kiel Auditorium, Assembly Hall 1
2:00 P.M.

Saturday, October 22

Council on Cardiovascular Surgery
Business Meeting
Kiel Auditorium, Assembly Hall 2
9:00 A.M.

Council on Community Service and Education
Luncheon and Business Meeting
Sheraton-Jefferson Hotel, Crystal Room
12:30 P.M.

Council on Circulation
Dinner
Sheraton-Jefferson Hotel, Room 1
6:15 P.M.

Sunday, October 23

Council on Basic Science
Luncheon and Business Meeting
Sheraton-Jefferson Hotel, Room 7
12:30 P.M.

Sunday, October23

ANNUAL DINNER
AMERICAN HEART ASSOCIATION
SHERATON-JEFFERSON HOTEL
Gold Room
7:30 P.M.

MONDAY, OCTOBER 24—All Day
12:00 Noon — Assembly Panels, Annual Luncheon } Sheraton-Jefferson Hotel

MONDAY, OCTOBER 24—All Day 12:00 Noon	Assembly Panels Annual Luncheon	}	Sheraton-Jefferson Hotel

Shantonu Lahiri
Amrut Tambekar

33rd SCIENTIFIC SESSIONS
of the AMERICAN HEART ASSOCIATION
Commemorating the Centenary of Willem Einthoven
October 21-23, 1960

CIRCULATION

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PROGRAM
of the
33rd SCIENTIFIC SESSIONS
Commemorating the Centenary of Willem Einthoven

KIEL AUDITORIUM, ST. LOUIS, MO.
OCTOBER 21-23, 1960

CONTENTS

Friday Morning	First Session on Clinical Cardiology	698
	Lewis A. Conner Memorial Lecture	698
	Symposium: Atrial Arrhythmias	698
	Simultaneous Scientific Sessions	698
	Council on Arteriosclerosis (I)	698
	Council on Rheumatic Fever and Congenital Heart Disease	699
Friday Afternoon	Second Session on Clinical Cardiology	700
	Panel on Current Therapy for Rheumatic Fever	700
	Simultaneous Scientific Sessions	700
	Council on Circulation	700
	Council on Arteriosclerosis (II)	701
	Council on Community Service and Education Jointly with American Dental Association	702
Friday Evening	"Fireside Conferences"	702
Saturday Morning	Third Session on Clinical Cardiology	703
	Symposium: Diagnosis and Treatment of Curable Hypertension	703
	Simultaneous Scientific Sessions	704
	Biophysical Methods in the Study of the Circulation	704
	Council on Cardiovascular Surgery (I)	705
	Council on Community Service and Education	705
	Session for Nurses (A.M.)	705
Saturday Afternoon	Fourth Session on Clinical Cardiology	705
	George E. Brown Memorial Lecture	706
	Simultaneous Scientific Sessions	706
	Council on Cardiovascular Surgery Jointly with Council on Rheumatic Fever and Congenital Heart Disease	706
	Symposium: Ventricular Septal Defects	706
	Council on High Blood Pressure Research	706
	Council on Community Service and Education	707
	Session for Nurses (P.M.)	707
Saturday Evening	Council on Community Service and Education	707
	Seminar on Nutrition	707

Sunday Morning	Fifth Session on Clinical Cardiology	707
	Symposium: Complete Heart Block	708
	Panel on Surgery for Extracranial Occlusive Cerebrovascular Disease	708
	Simultaneous Scientific Sessions	708
	Council on Basic Science (I)	708
	Symposium: Physiologic Basis of Pulmonary Function Tests	708
	Council on Community Service and Education	709
	Symposium: Nondietary Factors in Coronary Artery Disease	709
	Morning Session on Cardiovascular Films	709
Sunday Afternoon	Sixth Session on Clinical Cardiology	709
	Symposium: Lipids and Arteriosclerosis	709
	Simultaneous Scientific Sessions	710
	Council on Basic Science (II)	710
	Council on Cardiovascular Surgery (II)	711
	Symposium: Hypothermia and Extracorporeal Circulation	711
	Afternoon Session on Cardiovascular Films	711
Abstracts of Lectures		713
Abstracts *(Printed in alphabetical order according to senior author's name)*		714
Scientific Exhibits		837
Industrial Exhibits		842
Author's Index		848
List of Industrial Exhibitors		856

The program of the Annual Scientific Sessions of the American Heart Association is designed to meet the interests and wishes of practicing physicians, specialists in cardiovascular disease, and clinical and basic science investigators. It offers, within the time limitations of 3 days, a great variety of presentations competing for the participants' interest.

The Committee on Scientific Sessions Program has, after thorough consideration, selected the papers and broad subjects listed in the program. The Committee would welcome any comments regarding the content and format of these sessions, as well as constructive criticisms which may be useful in planning next year's scientific meetings.

AMERICAN HEART ASSOCIATION
1959-1960

COMMITTEE ON SCIENTIFIC SESSIONS PROGRAM

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HARRY FELDMAN, *Syracuse, N. Y.*
PAUL R. LURIE, *Indianapolis, Ind.*
SAUL J. ROBINSON, *San Francisco, Calif.*

SESSION ON BIOPHYSICAL METHODS IN STUDY OF CIRCULATION

CHARLES E. KOSSMANN, *New York, N. Y.,* CHAIRMAN
STANLEY A. BRILLER, *Philadelphia, Pa.*
W. PROCTOR HARVEY, *Washington, D. C.*
WILLIAM R. MILNOR, JR., *Baltimore, Md.*

Sessions on Clinical Cardiology were arranged by the Program Committee of the Council on Clinical Cardiology, jointly with the Councils on Cardiovascular Surgery, Circulation, Community Service and Education, High Blood Pressure, Research, and Rheumatic Fever and Congenital Heart Disease.

Symposium on Atrial Arrhythmias was arranged jointly by the Council on Clinical Cardiology of the American Heart Association and the American College of Cardiology.

P R O G R A M

TIME LIMIT FOR PRESENTATION OF PAPERS

Maximum is 10 Minutes for Presentation and 3 Minutes for Discussion

F R I D A Y M O R N I N G
OCTOBER 21, 1960

First Session on

CLINICAL CARDIOLOGY*

Opera House — 9:00 A.M. to 12:30 P.M.

Chairman
A. CARLTON ERNSTENE, *Cleveland, Ohio*

Co-Chairman
LEWIS E. JANUARY, *Iowa City, Iowa*

9:00 **COMMEMORATION OF THE CENTENARY OF BIRTH OF WILLEM EINTHOVEN**
GEORGE E. BURCH, *New Orleans, La.*

9:15 **LEWIS A. CONNER MEMORIAL LECTURE:**
PHYSIOLOGY OF CIRCULATION AS VIEWED BY THE INTERNIST.
EUGENE A. STEAD, JR., *Durham, N. C.*

SIMULTANEOUS SCIENTIFIC SESSIONS
Follow Immediately in Rooms as Indicated.

CLINICAL CARDIOLOGY SESSION
Continues Immediately in This Room.

10:00 ANNUAL BUSINESS MEETING OF THE COUNCIL

10:30 INTERMISSION

Joint Program with the

AMERICAN COLLEGE OF CARDIOLOGY

Chairman
A. CARLTON ERNSTENE, *Cleveland, Ohio*

Co-Chairman
JOHN S. LADUE, *New York, N. Y.*

10:45 EAR OXIMETRY IN CARDIAC DIAGNOSIS.
MALCOLM B. MCILROY, *San Francisco, Calif.*

11:05 OBJECTIVE EVIDENCE OF CARDIAC IMPAIRMENT: FUNCTIONAL TESTS.
ROBERT A. BRUCE, *Seattle, Wash.*

Symposium:

ATRIAL ARRHYTHMIAS

11:25 A.M. to 12:30 P.M.

11:25 MECHANISM.
GORDON K. MOE, *Utica, N. Y.*

11:50 BIOCHEMICAL CHANGES.
RICHARD BING, *Detroit, Mich.*

12:10 DIAGNOSIS.
E. GREY DIMOND, *La Jolla, Calif.*

SIMULTANEOUS SCIENTIFIC SESSIONS

Council on

ARTERIOSCLEROSIS (I)

Assembly Hall 1 — 10:00 A.M. to 12:30 P.M.

Chairman
FORREST E. KENDALL, *New York, N. Y.*

Co-Chairman
OTTO J. POLLAK, *Dover, Del.*

10:00 COMPARATIVE EFFECTS OF THYROXIN ANALOGS AS HYPOCHOLESTEROLEMIC AGENTS.
MAURICE M. BEST and CHARLES I. DUNCAN, *Louisville, Ky.*

* Category 2 postgraduate credit for members of the American Academy of General Practice.

0:15 FREQUENCY OF OVERWEIGHT, OBESITY, ELEVATED BLOOD PRESSURE AND SERUM CHOLESTEROL IN RAILROAD CLERKS AND SWITCHMEN.

HENRY L. TAYLOR, ANCEL KEYS, HENRY W. BLACKBURN, THOMAS C. PUCHNER, and JOSEPH BROZEK, *Minneapolis, Minn.*

0:30 HYPERLIPEMIA: TYPES AND DIFFERENTIAL DIAGNOSIS.

BURTON S. SKLARIN, WINNIFRED SEEGERS, and KURT HIRSCHHORN, *New York, N. Y.*

0:45 EFFECTS OF FEEDING FATS WITH VARYING FATTY ACID COMPOSITION ON THE BLOOD AND TISSUE LIPIDS OF CEBUS MONKEYS.

ROBERT W. WISSLER, RANDOLPH H. HUGHES, LAURENCE E. FRAZIER, and RICHARD A. RASMUSSEN, *Chicago, Ill.*

11:00 INTERMISSION

11:15 ANALYSIS OF THE FACTORS AFFECTING THE "RESTING" FREE FATTY ACID LEVEL IN NORMAL MAN.

ROBERT F. KLEIN, MORTON D. BOGDONOFF, E. HARVEY ESTES, and DAVID M. SHAW, *Durham, N. C.*

11:30 SPECIFICITY OF PLASMA FIBRINOGEN CHANGES FOR ATHEROSCLEROSIS.

L. O. PILGERAM, A. C. SCHRAM, and D. MILLS, *Minneapolis, Minn.*

11:45 CONTENT OF CEPHALINS IN THE PLASMA OF NORMAL SUBJECTS, PATIENTS WITH HYPERLIPEMIA AND HYPERCHOLESTEROLEMIA, AND PATIENTS WITH CORONARY HEART DISEASE.

MARTIN M. NOTHMAN and SAMUEL PROGER, *Boston, Mass.*

12:00 PLASMA HEPARIN LEVELS. NORMAL VALUES AND CORRELATION WITH SERUM CHOLESTEROL AND LOW-DENSITY LIPOPROTEINS.

HYMAN ENGELBERG, *Beverly Hills, Calif.*

Council on

RHEUMATIC FEVER AND CONGENITAL HEART DISEASE

Assembly Hall 2 — 10:00 A.M. to 12:30 P.M.

Chairman

JAMES W. DUSHANE, *Rochester, Minn.*

Co-Chairman

LOWELL A. RANTZ, *Palo Alto, Calif.*

10:00 EARLY MANIFESTATIONS OF THE CARDIOVASCULAR DISORDERS IN MARFAN SYNDROME.

ANGELOS C. PAPAIOANNOU, MAGNUS H. AGUSTSSON, and BENJAMIN M. GASUL, *Chicago, Ill.*

10:15 HYPOXIA AND FETAL CARDIOVASCULAR ANOMALIES.

BERNARD BAIRD and SHERBURNE F. COOK, *Berkeley, Calif.*

10:30 ISOLATED VENTRICULAR SEPTAL DEFECT OF THE PERSISTENT COMMON ATRIOVENTRICULAR CANAL TYPE.

HENRY N. NEUFELD, JACK L. TITUS, JAMES W. DUSHANE, HOWARD B. BURCHELL, and JESSE E. EDWARDS, *Rochester, Minn.*

10:45 USE OF A SHARP STYLET FOR INTERATRIAL SEPTAL PASSAGE OF THE RADIOPAQUE RIGHT HEART CATHETER INTO THE LEFT HEART.

DON L. FISHER, GEORGE R. LOGSDON, and MAURICE H. MCCAFFREY, *Pittsburgh, Pa.*

11:00 HEMODYNAMIC TECHNIC FOR THE DETECTION OF HYPERTROPHIC SUBAORTIC STENOSIS.

EDWIN C. BROCKENBROUGH and EUGENE BRAUNWALD, *Bethesda, Md.*

11:15 INTERMISSION

11:30 CONTROLLED STUDY OF STREPTOCOCCAL PHARYNGITIS IN CHILDREN: FACTORS RELATED TO THE ATTACK RATE OF RHEUMATIC FEVER.

ALAN C. SIEGEL, GENE H. STOLLERMAN, and ELOISE E. JOHNSON, *Chicago, Ill.*

11:45 INCIDENCE AND NATURE OF STREPTOCOCCAL INFECTION IN ADULT RHEUMATIC HEART DISEASE AS A BASIS FOR PENICILLIN PROPHYLAXIS.

JOSEPH M. MILLER, PAUL FREMONT-SMITH, and ROSE L. BREIHAHN, *Boston, Mass.*

12:00 RELATIONSHIP OF RHEUMATIC FEVER RECURRENCE RATE PER STREPTOCOCCAL INFECTION TO CLINICAL FEATURES IN THE PATIENT.

ANGELO TARANTA, ALVAN R. FEINSTEIN, HARRISON F. WOOD, and RITA SIMPSON, *Irvington-on-Hudson, N. Y.*

12:15 DEMONSTRATION OF PENICILLIN INHIBITION BY PHARYNGEAL FLORA IN PATIENTS TREATED FOR STREPTOCOCCAL PHARYNGITIS.

STANLEY H. BERNSTEIN, MAXWELL STILLERMAN, and CHARLES M. SAMET, *New Hyde Park, N. Y.*

FRIDAY AFTERNOON
OCTOBER 21, 1960

Second Session on

CLINICAL CARDIOLOGY

Arranged by the
COUNCIL ON CLINICAL CARDIOLOGY
and the COUNCIL ON
RHEUMATIC FEVER AND CONGENITAL HEART DISEASE

Opera House — 2:00 P.M. to 5:00 P.M.

Chairman
KATHERINE D. BROWNELL, *New York, N. Y.*

Co-Chairman
MICHAEL A. CORRADO, *Washington, D. C.*

2:00 PANEL ON CURRENT THERAPY FOR RHEUMATIC FEVER.
2:00 P.M. TO 2:45 P.M.

Moderator:
LOWELL A. RANTZ, *Palo Alto, Calif.*

Participants:
EDWARD FISCHEL, *New York, N. Y.*
CHARLES H. RAMMELKAMP, JR., *Cleveland, Ohio*
HARRISON F. WOOD, *Wallingford, Conn.*

2:45 FACTORS DETERMINING THE ATTACK RATE OF RHEUMATIC FEVER.
GENE H. STOLLERMAN, *Chicago, Ill.*

3:10 EVOLUTION OF RHEUMATIC HEART DISEASE IN CHILDREN: U.K.-U.S. COOPERATIVE CLINICAL TRIAL OF ACTH, CORTISONE, AND ASPIRIN.
DAVID D. RUTSTEIN, *Boston, Mass.*

3:30 INTERMISSION

3:45 ELECTROCARDIOGRAM IN LEFT-TO-RIGHT SHUNTS IN CONGENITAL HEART DISEASE.
JOHN KEITH, *Toronto, Canada*

4:00 EVALUATION OF THE RAPID DIAGNOSIS OF GROUP A STREPTOCOCCI BY FLUORESCENT ANTIBODY TECHNICS.
DONALD A. YARASHUS and ALAN C. SIEGEL, *Chicago, Ill.*

4:15 ATRIOVENTRICULAR NODAL TACHYCARDIA WITH BLOCK.
ALFRED PICK and RICHARD LANGENDORF, *Chicago, Ill.*

4:30 GRAHAM STEELL MURMUR VERSUS AORTIC REGURGITATION IN RHEUMATIC HEART DISEASE: RESULTS OF AORTIC VALVULOGRAPHY.
VINCENT RUNCO, WILLIAM MOLNAR, CHARLES V. MECKSTROTH, and JOSEPH M. RYAN, *Columbus, Ohio*

4:45 CONGENITAL HEART DISEASE IN THE FIFTH TO EIGHTH DECADES OF LIFE.
JUNE M. FISHER, WILLIAM R. WILSON, and ERNEST O. THEILEN, *Iowa City, Iowa*

SIMULTANEOUS SCIENTIFIC SESSIONS

Council on

CIRCULATION

Assembly Hall 1 — 2:00 P.M. to 5:00 P.M.

Chairman
WILLIAM GOLDRING, *New York, N. Y.*

Co-Chairman
ALBERT A. BRUST, *Cincinnati, Ohio*

2:00 HEMODYNAMIC EFFECTS OF FULL PHASE NEGATIVE PRESSURE BREATHING.
HYMAN W. PALEY, JAMES J. LEONARD, G. W. N. EGGERS, JR., WILLIAM J. DEGROOT, and JAMES V. WARREN, *Galveston, Texas*

2:15 CIRCULATORY ADAPTATIONS IN HEREDITARY ANEMIA.
GERARD M. TURINO, SYLVIA P. GRIFFITHS, SIDNEY BLUMENTHAL, JAMES A. WOLFF, and ALFRED P. FISHMAN, *New York, N. Y.*

2:30 EFFECTS OF TILTING ON PRESSURES, FLOW, AND VOLUME IN THE PULMONARY VASCULAR BED.
WILLIAM R. MILNOR and CHARLES J. MCGAFF, *Baltimore, Md.*

:45 HEMODYNAMIC AND MYOCARDIAL METABOLIC RESPONSE TO CIGARETTE SMOKING IN NORMAL AND CORONARY SUBJECTS.

TIMOTHY J. REGAN, *Jersey City, N. J.*, MARTIN J. FRANK, JOHN T. MCGINTY, *Detroit, Mich.*, HARPER K. HELLEMS, *Jersey City, N. J.*, and RICHARD J. BING, *Detroit, Mich.*

:00 RELATIONSHIP BETWEEN BLOOD CONCENTRATION OF NOREPINEPHRINE, CARDIAC OUTPUT, AND RESISTANCE.

ROBERT EICH, RICHARD CUDDY, HAROLD SMULYAN, and JOSEPH BARRY, *Syracuse, N. Y.*

3:15 EFFECT OF TOBACCO SMOKING ON THE CLOTTING PROCESS IN MAN AS MEASURED BY THROMBELASTOGRAPHY.

ORVILLE HORWITZ and DONALD S. WALDORF, *Philadelphia, Pa.*

3:30 INTERMISSION

3:45 STUDIES OF THE RELATION BETWEEN THE IN VIVO ANTITHROMBOTIC AND IN VITRO ANTICOAGULANT ACTIONS OF DICUMAROL.

DANIEL DEYKIN, STANFORD WESSLER, and STANLEY M. REIMER, *Boston, Mass.*

4:00 EFFECT OF VARIATIONS IN CARDIAC OUTPUT AND DIASTOLIC FILLING PERIOD UPON THE MITRAL DIASTOLIC GRADIENT.

PHILIP SAMET, LEONARD M. SILVERMAN, WILLIAM H. BERNSTEIN, and ROBERT S. LITWAK, *Miami Beach, Fla.*

:15 MYOCARDIAL INFARCTION AND ATRIAL ARRHYTHMIAS: CLINICAL, PATHOLOGIC AND EXPERIMENTAL STUDIES.

THOMAS N. JAMES, *Detroit, Mich.*

:30 VASOMOTOR RESPONSE OF THE VITAL ORGANS DURING CARDIAC ARRHYTHMIAS.

DAVID W. IRVING and ELIOT CORDAY, *Los Angeles, Calif.*

:45 REGIONAL FLOW-PRESSURE RELATIONSHIPS IN RESPONSE TO VASOACTIVE DRUGS IN THE INTACT DOG AND SHEEP.

N. S. ASSALI and A. WESTERSTEN, *Los Angeles, Calif.*

Council on

ARTERIOSCLEROSIS (II)

Assembly Hall 2 — 2:00 P.M. to 5:00 P.M.

Chairman
CAMPBELL MOSES, JR., *Pittsburgh, Pa.*

Co-Chairman
AARON KELLNER, *New York, N. Y.*

2:00 EFFECT OF LIPEMIA ON THE DISAPPEARANCE RATE OF INTRAVENOUSLY ADMINISTERED RADIOACTIVE FAT.

DONALD BERKOWITZ, JOHN J. SPITZER, MILLARD N. CROLL, and DAVID M. SKLAROFF, *Philadelphia, Pa.*

2:15 SERUM LIPIDS AND ARTERIOSCLEROSIS IN PROSTATIC CANCER PATIENTS.

GEORGE F. MEISSNER and CONSTANCE C. MOEHRING, *Providence, R. I.*

2:30 SERUM LIPIDS IN MEN RECEIVING HIGH CHOLESTEROL AND CHOLESTEROL-FREE DIETS.

WILLIAM E. CONNOR, ROBERT E. HODGES, and ROBERTA BLEILER, *Iowa City, Iowa*

2:45 VASCULARIZATION OF IN SITU AND INTRAOCULARLY TRANSPLANTED ATHEROMATOUS PLAQUES IN RABBITS.

A. C. HIGGINBOTHAM and F. H. HIGGINBOTHAM, *Morgantown, W. Va.*

3:00 BIOCHEMICAL STUDIES IN FULL-BLOODED NAVAJO INDIANS: II. LIPIDS AND LIPOPROTEINS.

ROBERT J. KOSITCHEK, MOSES WURM, and REUBEN STRAUS, *Burbank, Calif.*

3:15 INTERMISSION

3:30 CORONARY ARTERIAL CALCIFICATION.

DAVID H. BLANKENHORN, *Los Angeles, Calif.*

3:45 PROGNOSIS AND SERUM LIPIDS IN SURVIVORS OF MYOCARDIAL INFARCTION.

ROBERT D. ROE, ALICK LITTLE, and HENRY M. SHANOFF, *Toronto, Canada*

4:00 INTERRELATION OF CORONARY OCCLUSION, INTERCORONARY ANASTOMOSIS, MYOCARDIAL INFARCTION AND ANGINA PECTORIS IN 250 PATIENTS.

ROBERT B. ALLISON, FELIX L. RODRIGUEZ, WALTER H. ABELMANN, and LAURENCE B. ELLIS, *Boston, Mass.*

4:15 FREQUENCY OF CORONARY THROMBI AS RELATED TO DURATION OF SURVIVAL FROM THE ONSET OF ACUTE FATAL EPISODES OF MYOCARDIAL ISCHEMIA.

DAVID M. SPAIN, *Brooklyn, N. Y.*, and VICTORIA A. BRADESS, *Valhalla, N. Y.*

4:30 CLINICOPATHOLOGIC STUDY OF THE FEASIBILITY OF DIRECT SURGICAL TREATMENT FOR OCCLUSIVE CORONARY-ARTERY DISEASE.

HARRY A. SWEDLUND, RICHARD W. P. ACHOR, and JESSE E. EDWARDS, *Rochester, Minn.*

Council on

COMMUNITY SERVICE AND EDUCATION

Jointly with

AMERICAN DENTAL ASSOCIATION

MEDICAL-DENTAL SESSION

Assembly Hall 3 — 2:00 P.M. to 5:00 P.M.

For detailed information, see last page of Program.

FRIDAY EVENING
OCTOBER 21, 1960

"FIRESIDE CONFERENCES"

American Heart Association

Jointly with the

American College of Cardiology

8:30 P.M. to 10:30 P.M.

Sheraton-Jefferson Hotel

Conference nos. 1-13

1. NEW DRUGS IN THE TREATMENT OF HYPERTENSION.

WALTER M. KIRKENDALL, *Iowa City, Iowa*, EDWARD D. FREIS, *Washington, D. C.*, and JOHN H. MOYER, *Philadelphia, Pa.* (ROOM 1)

2. SURGERY FOR INSUFFICIENT VALVULAR LESIONS.

C. A. HUFNAGEL, *Washington, D. C.*, HENRY ZIMMERMAN, *Cleveland, Ohio*, and ROBERT GLOVER, *Philadelphia, Pa.* (ROOM 2)

3. SURGERY FOR STENOTIC VALVULAR LESIONS.

J. L. EHRENHAFT, *Iowa City, Iowa*, DWIGHT E. HARKEN, *Boston, Mass.*, and W. M. LIKOFF, *Philadelphia, Pa.* (ROOM 3)

4. PULMONARY HYPERTENSION AS A LIMITING FACTOR IN SURGERY FOR CONGENITAL HEART DISEASE.

C. WALTON LILLEHEI, *Minneapolis, Minn.*, H. W. MARSHALL, *Rochester, N. Y.*, and S. FRANK REDO, *New York, N. Y.* (ROOM 4)

5. MAJOR VESSEL REPLACEMENT.

MICHAEL E. DE BAKEY, *Houston, Texas*, EDGAR V. ALLEN, *Rochester, Minn.*, and A. W. HUMPHRIES, *Cleveland, Ohio* (SOUTH ROOM)

6. TREATMENT OF CARDIAC ARRHYTHMIAS.

SAMUEL S. BELLET, *Philadelphia, Pa.*, REUBEN BERMAN, *Minneapolis, Minn.*, and ELIOT CORDAY, *Los Angeles, Calif.* (ROOM 6)

7. PROBLEMS IN THE CONTROL OF ANTICOAGULANT THERAPY: INDICATIONS AND LIMITATIONS.

KENNETH H. BRINKHOUS, *Chapel Hill, N. C.*, IRVING S. WRIGHT, *New York, N. Y.*, and ROBERT G. SIEKERT, *Rochester, Minn.* (ROOM 7)

8. FIBRINOLYSIS IN PRACTICE.

EUGENE E. CLIFFTON, *New York, N. Y.*, OSCAR RATNOFF, *Cleveland, Ohio*, and ANTHONY FLETCHER, *St. Louis, Mo.* (ROOM 8)

9. TREATMENT OF CARDIOGENIC SHOCK.

JOHN SAMPSON, *San Francisco, Calif.*, RICHARD LYONS, *Syracuse, N. Y.*, and LYSLE H. PETERSON, *Philadelphia, Pa.* (ROOM 9)

10. OFFICE DIAGNOSIS OF CONGENITAL HEART DISEASE.

ALEXANDER S. NADAS, *Boston, Mass.* BENJAMIN M. GASUL, *Chicago, Ill.* and HOWARD B. BURCHELL, *Rochester, Minn.* (IVORY ROOM)

11. MANAGEMENT OF ANGINA PECTORIS.

GEORGE C. GRIFFITH, *Los Angeles Calif.*, HERRMAN L. BLUMGART, *Boston, Mass.*, and LOUIS F. BISHOP, *New York, N. Y.* (IVORY ROOM)

13. METHODS FOR THE MANAGEMENT OF HYPERLIPEMIA.

HERBERT POLLACK, *New York, N. Y.*, JEREMIAH STAMLER, *Chicago, Ill.*, and ROBERT E. OLSON, *Pittsburgh, Pa.* (GOLD ROOM)

14. RECENT ADVANCES IN DIAGNOSIS AND TREATMENT OF RHEUMATIC FEVER.

GENE H. STOLLERMAN, *Chicago, Ill.*, MILTON S. SASLAW, *Miami, Fla.*, and JOSEPH M. MILLER, *Boston, Mass.* (GOLD ROOM)

Statler-Hilton Hotel

Conference nos. 14-25

14. APPLIED PHONOCARDIOGRAPHY.

VICTOR A. MCKUSICK, *Baltimore, Md.*, J. SCOTT BUTTERWORTH, *New York, N. Y.*, and ALDO A. LUISADA, *Chicago, Ill.* (FOYER I)

15. CARDIAC FUNCTION TESTS.

ROBERT A. BRUCE, *Seattle, Wash.*, RICHARD GORLIN, *Boston, Mass.*, and ISAAC STARR, *Philadelphia, Pa.* (FOYER II)

16. REFRACTORY CARDIAC FAILURE.

CHARLES A. R. CONNOR, *New York, N. Y.*, E. GREY DIMOND, *La Jolla, Calif.*, and ALBERT RUBIN, *New York, N. Y.* (FOYER III)

17. EVALUATION OF RADIOGRAPHIC TECHNICS IN CARDIOVASCULAR DISEASE.

F. MASON SONES, JR., *Cleveland, Ohio*, ISRAEL STEINBERG, *New York, N. Y.*, and LOUIS A. SOLOFF, *Philadelphia, Pa.* (BALLROOM)

18. SURGICAL TREATMENT OF CORONARY HEART DISEASE.

CHARLES P. BAILEY, *New York, N. Y.*, ARTHUR M. VINEBERG, *Montreal, Canada*, and STACEY B. DAY, *Minneapolis, Minn.* (LOS ANGELES ROOM)

19. CARDIAC RESUSCITATION.

HUGH E. STEVENSON, *Columbia, Mo.*, OSLER A. ABBOTT, *Atlanta, Ga.*, and PAUL M. ZOLL, *Boston, Mass.* (WASHINGTON ROOM)

20. EVALUATION OF TECHNICS FOR MEASURING CARDIAC OUTPUT.

EUGENE BRAUNWALD, *Bethesda, Md.*, EARL H. WOOD, *Rochester, Minn.*, and LEWIS DEXTER, *Boston, Mass.* (DALLAS ROOM)

21. DIFFERENTIAL DIAGNOSIS OF CARDIOGENIC PAIN.

E. COWLES ANDRUS, *Baltimore, Md.*, EDGAR HULL, *New Orleans, La.*, and SIMON DACK, *New York, N. Y.* (CLEVELAND ROOM)

22. EFFECT OF ENVIRONMENT AND STRESS UPON PATIENTS WITH CARDIOVASCULAR DISEASE.

GEORGE E. BURCH, *New Orleans, La.*, HERMAN K. HELLERSTEIN, *Cleveland, Ohio*, and STEWART G. WOLF, *Oklahoma City, Okla.* (DETROIT ROOM)

23. CHANGES IN MYOCARDIAL METABOLISM IN HEART DISEASE.

RICHARD J. BING, *Detroit, Mich.*, DONALD E. GREGG, *Washington, D. C.*, and WILLIAM H. DANFORTH, *St. Louis, Mo.* (MISSOURI ROOM)

24. PLACE OF VECTORCARDIOGRAPHY IN THE PRACTICE OF CARDIOLOGY.

ROBERT P. GRANT, *Bethesda, Md.*, DEMETRIO SODI-PALLARES, *Mexico City, Mexico*, and ARTHUR GRISHMAN, *New York, N. Y.* (DANIEL BOONE ROOM)

25. MANAGEMENT OF COR PULMONALE.

GEORGE R. MENEELY, *Nashville, Tenn.*, G. W. H. SCHEPERS, *Wilmington, Del.*, and J. L. PATTERSON, JR., *Richmond, Va.* (ST. CHARLES ROOM)

SATURDAY MORNING

OCTOBER 22, 1960

Third Session on

CLINICAL CARDIOLOGY

Arranged by the

COUNCIL ON CLINICAL CARDIOLOGY

and the COUNCIL ON

HIGH BLOOD PRESSURE RESEARCH

Opera House — 9:00 A.M. to 12:00 Noon

Chairman

FRANCIS L. CHAMBERLAIN, *San Francisco, Calif.*

Co-Chairman

KENNETH G. KOHLSTAEDT, *Indianapolis, Ind.*

Symposium:

PROBLEMS IN THE DIAGNOSIS AND TREATMENT OF CURABLE HYPERTENSION

9:00 A.M. to 10:30 A.M.

Moderator

SIBLEY W. HOOBLER, *Ann Arbor, Mich.*

9:00 RENAL ARTERIAL DISEASE.

EUGENE F. POUTASSE, *Cleveland, Ohio*

9:20 PHEOCHROMOCYTOMA.
GRACE M. ROTH, *Albuquerque, N. M.*

9:35 PRIMARY ALDOSTERONISM.
JEROME W. CONN, *Ann Arbor, Mich.*

9:55 COARCTATION OF THE AORTA.
JOHN W. ECKSTEIN, *Iowa City, Iowa*

10:10 CHRONIC PYELONEPHRITIS.
ROBERT M. KARK, *Chicago, Ill.*

10:30 INTERMISSION

10:45 RELATIONSHIP BETWEEN ARTERIAL PRESSURE AND EXERTIONAL ANGINA PECTORIS IN HYPERTENSIVE PATIENTS.
A. J. GEORGOPOULOS, F. MASON SONES, JR., and I. H. PAGE, *Cleveland, Ohio*

11:00 CLINICAL EXPERIENCE WITH A NEW ANTIHYPERTENSIVE AGENT—GUANETHIDINE.
JOHN T. EAGAN and EDWARD S. ORGAIN, *Durham, N. C.*

11:15 CHANGES IN MORTALITY RATES OF SURGICALLY AND MEDICALLY TREATED PATIENTS WITH HYPERTENSIVE DISEASE OVER A TEN-YEAR PERIOD.
DERA KINSEY, HERBERT SISE, GEORGE P. WHITELAW, RAYMOND WALTHER, and REGINALD H. SMITHWICK, *Boston, Mass.*

11:30 INTERRELATION BETWEEN CORONARY HEMODYNAMICS AND THE ELECTROCARDIOGRAM DURING EXERCISE.
RICHARD J. WAGMAN, JOSEPH V. MESSER, HERBERT J. LEVINE, WILLIAM A. NEILL, and RICHARD GORLIN, *Boston, Mass.*

11:45 PRECORDIAL ELECTROCARDIOGRAM DURING EXERCISE.
RAMON F. ABARQUEZ, ALVIN H. FREIMAN, FREDRIC REICHEL, and JOHN S. LADUE, *New York, N. Y.*

SIMULTANEOUS SCIENTIFIC SESSIONS

BIOPHYSICAL METHODS IN THE STUDY OF THE CIRCULATION

Assembly Hall 1 — 9:00 A.M. to 12:00 Noon

Chairman
CHARLES E. KOSSMANN, *New York, N. Y.*

Co-Chairman
WILLIAM R. MILNOR, *Baltimore, Md.*

9:00 NEW ANGIOCARDIOGRAPHIC SIGN OF AORTIC REGURGITATION: ITS UTILIZATION FOR THE MEASUREMENT OF REGURGITANT FLOW.
RENE A. ARCILLA, MAGNUS H. AGUSTSSON, ZWI STEIGER, and BENJAMIN M. GASUL, *Chicago, Ill.*

9:15 SELECTIVE LEFT HEART CINECARDIOANGIOGRAPHY IN THE DIAGNOSIS OF ACQUIRED HEART DISEASE.
WALTER E. JUDSON, EUGENE C. KLATTE, and NANCY H. RAUSCH, *Indianapolis, Ind.*

9:30 STROKE VOLUME AND CARDIAC OUTPUT MEASUREMENT IN THE INTACT ANIMAL WITH AN ELECTROMAGNETIC FLOWMETER.
JULIEN I. E. HOFFMAN, ABRAHAM GUZ, R. ROLLA SPOTTS, and WILLIAM L. WEIRICH, *San Francisco, Calif.*

9:45 LEFT VENTRICULAR EJECTION VELOCITY AND ACCELERATION STUDIES IN INTACT MAN.
SAMUEL M. FOX, III, G. OCTO BARNETT, ALEXANDER J. MALLOS, DONALD L. FRY, and JOSEPH C. GREENFIELD, JR., *Bethesda, Md.*

10:00 DIAGNOSIS OF PERICARDIAL EFFUSION BY RADIOISOTOPE SCANNING.
HENRY N. WAGNER, JR., JOHN G. MCAFEE, and JAMES M. MOZLEY, *Baltimore, Md.*

10:15 DIAGNOSIS OF CONGENITAL HEART DISEASE FROM CLINICAL DATA USING A DIGITAL COMPUTER.
HOMER R. WARNER, L. GEORGE VEASY, ALAN F. TORONTO, and ROBERT E. STEPHENSON, *Salt Lake City, Utah*

10:30 INTERMISSION

10:45 CLINICAL APPRAISAL OF THE VECTORCARDIOGRAM IN 207 CASES OF MYOCARDIAL INFARCTION (FRANK SYSTEM).
PAUL G. HUGENHOLTZ, CLAUDE E. FORKNER, JR., and HAROLD D. LEVINE, *Boston, Mass.*

11:00 COMPARATIVE PROXIMITY AND REMOTENESS CHARACTERISTICS OF CONVENTIONAL ELECTROCARDIOGRAPHIC LEADS: RELATIONSHIP TO THE ELECTROPOSITION CONCEPT.
JOHN W. EVANS, BLAIR D. ERB, and DANIEL A. BRODY, *Memphis, Tenn.*

11:15 EFFECTS OF LOW OXYGEN TENSION AND OF ISCHEMIA ON CARDIAC CONDUCTION.
ALBIN A. BAGDONAS, JACKSON H. STUCKEY, BRIAN F. HOFFMAN, JUAN PIERA, and NORMAN S. AMER, *Brooklyn, N. Y.*

11:30 APPLICATION OF AN INTRAVASCULAR ELECTRODE FOR THE RECORDING OF INDICATOR-DILUTION CURVES.
PETER L. FROMMER, WILLIAM W. PFAFF, EUGENE BRAUNWALD, and ANDREW G. MORROW, *Bethesda, Md.*

11:45 HYDROGEN-PLATINUM ELECTRODE SYSTEM IN DETECTION OF CARDIAC SHUNTS.
ALBERT L. HYMAN, EDWARD S. HYMAN, ANTHONY QUIROZ, and JAMES GANTT, *New Orleans, La.*

Council on

CARDIOVASCULAR SURGERY (I)

Assembly Hall 2 — 9:00 A.M. to 12:00 Noon

Chairman
FRANK L. GERBODE, *San Francisco, Calif.*

Co-Chairman
WILLIAM W. L. GLENN, *New Haven, Conn.*

9:00 FOUR-YEAR EVALUATION OF SURGICAL CORRECTION OF MITRAL REGURGITATION BY THE OPEN TECHNIC.
EARLE B. KAY and H. A. ZIMMERMAN, *Cleveland, Ohio*

9:15 REPORT ON THE TREATMENT OF THREE PATIENTS WITH AORTIC INSUFFICIENCY AND VENTRICULAR SEPTAL DEFECT BY PLICATION OF A PROLAPSED AORTIC VALVE CUSP.
FRANK C. SPENCER, HENRY T. BAHNSON, and CATHERINE A. NEILL, *Baltimore, Md.*

9:30 PRE- AND POSTOPERATIVE ASSESSMENT OF AORTIC STENOSIS.
MARTIN LEES, ANNA J. HAUCK, ABRAHAM M. RUDOLPH, ALEXANDER S. NADAS, and ROBERT E. GROSS, *Boston, Mass.*

9:45 SIGNIFICANCE OF ATRIAL FIBRILLATION AND ARTERIAL EMBOLIZATION IN RHEUMATIC MITRAL VALVE DISEASE.
RODMAN E. TABER and CONRAD R. LAM, *Detroit, Mich.*

10:00 SURGICAL TREATMENT OF AORTIC AND MITRAL VALVE LESIONS UTILIZING PROSTHESES.
C. WALTON LILLEHEI, DAVID M. LONG, JR., ROBERT D. SELLERS, and RICHARD L. VARCO, *Minneapolis, Minn.*

10:15 SURGICAL TREATMENT OF RENOVASCULAR HYPERTENSION.
GEORGE C. MORRIS, JR., MICHAEL E. DE BAKEY, DENTON A. COOLEY, and E. STANLEY CRAWFORD, *Houston, Texas*

10:30 INTERMISSION

10:45 MICRO-VASCULAR SURGERY: NEW HORIZON IN CORONARY ARTERY SURGERY.
JULIUS H. JACOBSON, II, DONALD B. MILLER, and ERNESTO SUAREZ, *Burlington, Vt.*

11:00 POSTVENTRICULOTOMY RIGHT BUNDLE-BRANCH BLOCK: ITS ETIOLOGY.
C. JOAN COGGIN, ELLSWORTH E. WAREHAM, and RONALD H. SELVESTER, *Los Angeles, Calif.*

11:15 CARDIAC ARRHYTHMIAS FOLLOWING INTRACARDIAC SURGERY.
MICHAEL D. RABBINO, *New York, N. Y.*, LEONARD S. DREIFUS, and WILLIAM LIKOFF, *Philadelphia, Pa.*

11:30 EFFECT OF TEMPERATURE ON VENTRICULAR FUNCTION IN THE DOG WITH COMPLETE HEART BLOCK.
VALLEE L. WILLMAN, HECTOR S. HOWARD, and C. ROLLINS HANLON, *St. Louis, Mo.*

11:45 PHYSIOLOGIC STUDIES IN PATIENTS WITH PARTIAL SURGICAL CORRECTION OF TRANSPOSITION OF THE GREAT VESSELS.
MILTON H. PAUL, ROBERT A. MILLER, and THOMAS G. BAFFES, *Chicago, Ill.*

Council on

COMMUNITY SERVICE AND EDUCATION

SESSION FOR NURSES (A.M.)

Assembly Hall 3 — 9:30 A.M. to 12:00 Noon

For detailed information,
see last page of Program.

SATURDAY AFTERNOON
OCTOBER 22, 1960

Fourth Session on

CLINICAL CARDIOLOGY

Arranged by the
COUNCIL ON CLINICAL CARDIOLOGY
and the
COUNCIL ON CIRCULATION

Opera House — 2:00 P.M. to 5:00 P.M.

Chairman
HERBERT CHASIS, *New York, N. Y.*

Co-Chairman
WRIGHT R. ADAMS, *Chicago, Ill.*

2:00 PRESENTATION OF ALBERT LASKER AWARD
TO
KARL PAUL LINK
EDGAR V. ALLEN
IRVING S. WRIGHT

2:15 **GEORGE E. BROWN MEMORIAL LECTURE:**

CLINICAL PHYSIOLOGY OF THE SPLANCHNIC CIRCULATION.

STANLEY E. BRADLEY, *New York, N. Y.*

SIMULTANEOUS SCIENTIFIC SESSIONS
Follow Immediately in Rooms as Indicated.

CLINICAL CARDIOLOGY SESSION
Continues Immediately in This Room.

3:10 CLINICAL SIGNIFICANCE OF THE PULMONARY COLLATERAL CIRCULATION.

ALFRED P. FISHMAN, *New York, N. Y.*

3:30 INTERMISSION

3:45 EVIDENCE FOR THE PRODUCTION OF A RIGHT-TO-LEFT SHUNT BY AUTOLOGOUS PULMONARY EMBOLI.

MYRON STEIN, CLAUDE E. FORKNER, JR., *Boston, Mass.*, EUGENE D. ROBIN, *Pittsburgh, Pa.*, GEORGE S. KURLAND, and STANFORD WESSLER, *Boston, Mass.*

4:00 RECURRENT PULMONARY EMBOLISM AS A REMEDIABLE CAUSE OF CHRONIC HEART FAILURE.

EDWARD A. EDWARDS, LEWIS DEXTER, and WILLIAM C. DONAHUE, *Boston, Mass.*

4:15 PULMONARY ARTERIOVENOUS FISTULAS: PHYSIOLOGIC AND CLINICAL CONSIDERATIONS.

JOHN H. MOYER and ALBERT N. BREST, *Philadelphia, Pa.*

4:30 SURGICAL STUDIES OF THE LYMPHATICS.

CALLISTO DANESE and JOHN M. HOWARD, *Philadelphia, Pa.*

4:45 FALL OF SERUM POTASSIUM CONCENTRATION AND APPEARANCE OF CARDIAC ARRHYTHMIAS DURING INFUSION OF POTASSIUM WITH GLUCOSE IN PATIENTS WITH HYPOPOTASSEMIA.

ARTHUR S. KUNIN, BORYS SURAWICZ, and ETHAN A. SIMS, *Burlington, Vt.*

SIMULTANEOUS SCIENTIFIC SESSIONS

Council on

CARDIOVASCULAR SURGERY

Jointly with

Council on

RHEUMATIC FEVER AND CONGENITAL HEART DISEASE

Assembly Hall 1 — 3:00 P.M. to 5:30 P.M.

Chairman
OSCAR CREECH, *New Orleans, La.*

Co-Chairman
EDWARD C. LAMBERT, *Buffalo, N. Y.*

Symposium:

VENTRICULAR SEPTAL DEFECTS

3:00 P.M. to 4:00 P.M.

Moderator:
HENRY SWAN, *Denver, Colo.*

3:00 MEDICAL ASPECTS.

JAMES W. DUSHANE, *Rochester, Minn.*

3:15 RADIOLOGIC ASPECTS.

RICHARD GREENSPAN, *New Haven, Conn.*

3:30 SURGICAL ASPECTS.

C. ROLAND HANLON, *St. Louis, Mo.*

3:45 DISCUSSION

4:00 INTERMISSION

4:15 PATHOLOGIC METHODS FOR THE STUDY OF THE ENTIRE CONGENITALLY MALFORMED HEART FOR ELECTROCARDIOGRAPHIC AND PHYSIOLOGIC CORRELATION.

MAURICE LEV and URSULA F. ROWLATT, *Chicago, Ill.*

4:30 EIGHT-YEAR EVALUATION OF THE DAM-MANN-MULLER PROCEDURE.

JAMES A. MCEACHEN and RODNEY T. SMITH, *Santa Monica, Calif.*

4:45 CIRCULATORY BYPASS OF THE RIGHT SIDE OF THE HEART: VI. SUPERIOR VENA CAVA-RIGHT PULMONARY ARTERY ANASTOMOSIS: EXPERIMENTAL BACKGROUND AND CLINICAL APPLICATION.

WILLIAM W. L. GLENN, NELSON K. ORDWAY, REMEDIOS SUNICO, RUTH WHITTEMORE, and MARIE J. BROWNE, *New Haven, Conn.*

5:00 SUPRAVALVULAR AORTIC STENOSIS: EXPERIENCES WITH THREE YOUNG MALES.

CHARLES F. WOOLEY, DON M. HOSIER, RICHARD W. BOOTH, WILLIAM MOLNAR, HOWARD D. SIRAK, and JOSEPH M. RYAN, *Columbus, Ohio*

5:15 ENDOCARDIAL CUSHION DEFECTS: DIAGNOSIS AND TECHNIC OF SURGICAL REPAIR.

FRANK GERBODE, J. BRUCE JOHNSTON, SAUL ROBINSON, GEORGE A. HARKINS, and JOHN J. OSBORN, *San Francisco, Calif.*

Council on

HIGH BLOOD PRESSURE RESEARCH

Assembly Hall 2 — 3:00 P.M. to 5:30 P.M.

Chairman
EDWARD D. FREIS, *Washington, D. C.*

Co-Chairman
MILTON MENDLOWITZ, *New York, N. Y.*

3:00 ANGIOTENSIN SKIN TEST IN NORMOTENSIVE AND HYPERTENSIVE HUMANS.

BENJAMIN JABLONS, *New York, N. Y.*, PAQUITA E. MANULAT, *Cebu, Philippine Islands*, EIN S. HAHN, *Seoul, Korea*, PANYA NAKVANICH, *Bangkok, Thailand*, and ROSARIO C. SALVO, *Manila, Philippine Islands*

3:15 DIGITAL VASCULAR REACTIVITY TO HYPERTENSIN II IN NORMOTENSIVE SUBJECTS AND IN PATIENTS WITH PRIMARY HYPERTENSION.

MILTON MENDLOWITZ, NOSRAT NAFTCHI, ROBERT L. WOLF, and STANLEY E. GITLOW, *New York, N. Y.*

3:30 HEMODYNAMIC EFFECTS OF ANGIOTENSIN IN MAN.

PAUL N. YU, MILTON N. LURIA, JAMES K. FINLAYSON, and C. ALPHEUS STANFIELD, *Rochester, N. Y.*

3:45 RELEASE OF RENAL PRESSOR SUBSTANCE IN HYPERTENSIVE RATS.

GEORGES M. C. MASSON and TERUO OMAE, *Cleveland, Ohio*

4:00 INTERMISSION

4:15 SUSCEPTIBILITY OF RENAL HYPERTENSIVE RATS TO PYELONEPHRITIS AND THE PREDISPOSITION OF PYELONEPHRITIC RATS TO HYPERTENSION.

ALVIN P. SHAPIRO and JEAN L. KOBERNICK, *Pittsburgh, Pa.*

4:30 PREDICTIVE TESTS IN UNILATERAL RENAL HYPERTENSION: CRITICAL ANALYSIS OF TWENTY-FIVE OPERATED PATIENTS.

MORTON H. MAXWELL, ROBERT E. ROCKNEY, CHESTER C. WINTER, and CHARLES R. KLEEMAN, *Los Angeles, Calif.*

4:45 BODY FLUID AND ELECTROLYTE COMPOSITION IN PRIMARY HYPERALDOSTERONISM.

ARAM V. CHOBANIAN and WILLIAM HOLLANDER, *Boston, Mass.*

5:00 EFFECT OF THIAZIDE DIURETICS ON PLASMA VOLUME, BODY ELECTROLYTES AND EXCRETION OF ALDOSTERONE OF HYPERTENSIVE PATIENTS.

RAY W. GIFFORD, JR., VERNON R. MATTOX, ALAN L. ORVIS, DON R. MATHIESON, and HAROLD L. MASON, *Rochester, Minn.*

5:15 INTRAVASCULAR VOLUME AS A DETERMINANT OF ARTERIAL PRESSURE AND SYMPATHETIC VASOMOTOR TONE.

HARRIET P. DUSTAN and HIDEO TAKAGI, *Cleveland, Ohio*

Council on

COMMUNITY SERVICE AND EDUCATION

SESSION FOR NURSES (P.M.)

Assembly Hall 3 — 2:00 P.M. to 5:00 P.M.

For detailed information, see last page of Program.

SATURDAY EVENING
OCTOBER 22, 1960

Council on

COMMUNITY SERVICE AND EDUCATION

Statler-Hilton Hotel, Missouri Room

8:00 P.M. to 10:00 P.M.

SEMINAR ON NUTRITION (for Heart Association Affiliate and Chapter Representatives)

Chairman
HERBERT POLLACK, *New York, N. Y.*

Co-Chairman
THEODORE VAN ITALLIE, *New York, N. Y.*

Participants:
FRANCISCO GRANDE, *Minneapolis, Minn.*
PHILIP L. WHITE, *Chicago, Ill.*
PAULINE MURRAH, *Armonk, N. Y.*

SUNDAY MORNING
OCTOBER 23, 1960

Fifth Session on

CLINICAL CARDIOLOGY

Arranged by the
COUNCIL ON CLINICAL CARDIOLOGY
and the
COUNCIL ON CARDIOVASCULAR SURGERY

Opera House — 9:00 A.M. to 12:00 Noon

Chairman
JAMES V. WARREN, *Galveston, Texas*

Co-Chairman
CHARLES HUFNAGEL, *Washington, D. C.*

Symposium:

COMPLETE HEART BLOCK

9:00 A.M. to 10:00 A.M.

Moderator:
EDWARD MASSIE, *St. Louis, Mo.*

9:00 ANATOMY OF THE CONDUCTIVE SYSTEM IN NORMAL HEARTS AND CONGENITAL DEFECTS.
MAURICE LEV, *Chicago, Ill.*

9:20 THERAPY OF COMPLETE HEART BLOCK: MEDICAL ASPECTS.
EDWARD MASSIE, *St. Louis, Mo.*

9:40 SURGICAL ASPECTS.
WILLIAM WEIRICH, *San Francisco, Calif.*

10:00 PANEL ON SURGERY FOR EXTRACRANIAL OCCLUSIVE CEREBROVASCULAR DISEASE. 10:00 A.M. to 11:00 A.M.

Moderator:
MAURICE W. VAN ALLEN, *Iowa City, Iowa*

Participants:
E. S. GURDJIAN, *Detroit, Mich.*
JUAN M. TAVERAS, *New York, N. Y.*
E. STANLEY CRAWFORD, *Houston, Texas*

11:00 INTERMISSION

11:15 DIFFERENTIAL DIAGNOSIS OF CONTINUOUS MURMURS SUGGESTING A PATENT DUCTUS ARTERIOSUS.
HENRY D. MCINTOSH, JULIAN C. SLEEPER, HOWARD K. THOMPSON, JR., WILLIAM F. BARRY, and EDWARD S. ORGAIN, *Durham, N. C.*

11:30 SYSTEMIC AND PULMONARY EMBOLISMS BEFORE AND AFTER MITRAL COMMISSUROTOMY.
FREDERICK KELLOGG, I. WILLIAM FISHMAN, *Long Beach, Calif.*, CHI KONG LIU, and ROGER LARSON, *Torrance, Calif.*

11:45 POSTPERICARDIOTOMY SYNDROME FOLLOWING TRAUMATIC HEMOPERICARDIUM.
BERNARD TABATZNIK and JAMES P. ISAACS, *Baltimore, Md.*

12:00 TEN-YEAR STATUS AFTER SYMPATHECTOMY FOR ARTERIOSCLEROSIS.
EDWARD A. EDWARDS, *Boston, Mass.*, and CHILTON CRANE, *Brookline, Mass.*

12:15 SURGICAL CONSIDERATIONS OF OCCLUSIVE DISEASE OF THE GREAT VESSELS ARISING FROM THE AORTIC ARCH.
MICHAEL E. DE BAKEY, E. STANLEY CRAWFORD, DENTON A. COOLEY, GEORGE C. MORRIS, JR., and WALTER S. HENLY, *Houston, Texas*

SIMULTANEOUS SCIENTIFIC SESSIONS

Council on

BASIC SCIENCE (I)

Assembly Hall 1 — 9:00 A.M. to 12:00 Noon

Chairman
EARL H. WOOD, *Rochester, Minn.*

Co-Chairman
LYSLE H. PETERSON, *Philadelphia, Pa.*

Symposium:

PHYSIOLOGIC BASIS OF PULMONARY FUNCTION TESTS

9:00 A.M. to 11:00 A.M.

Moderator:
WARD S. FOWLER, *Rochester, Minn.*

9:00 INTRODUCTORY REMARKS.
WARD S. FOWLER, *Rochester, Minn.*

9:10 RESPIRATORY MECHANICS.
JERE MEAD, *Boston, Mass.*

9:35 INTRAPULMONARY GAS DISTRIBUTION.
ALBERT ROOS, *St. Louis, Mo.*

10:00 CENTRAL CIRCULATION.
ALFRED P. FISHMAN, *New York, N. Y.*

10:25 OXYGEN AND CARBON DIOXIDE EXCHANGE.
ROBERT E. FORSTER, *Philadelphia, Pa.*

10:50 DISCUSSION

11:00 INTERMISSION

11:15 CORONARY SINUS METHOD AS AN ADEQUATE MEASURE OF LEFT VENTRICULAR CORONARY FLOW AND METABOLISM.
ROBERT LAFONTANT, HAROLD FEINBERG, and LOUIS N. KATZ, *Chicago, Ill.*

11:30 VENOUS DRAINAGE OF THE SEPTAL ARTERY OF THE DOG.
THOMAS W. MOIR and RICHARD W. ECKSTEIN, *Cleveland, Ohio*

11:45 EFFECT OF SEROTONIN ON CORONARY VASCULAR RESISTANCE AND MYOCARDIAL OXYGEN CONSUMPTION.
DOUGLAS M. GRIGGS, JR., and ROBERT B. CASE, *New York, N. Y.*

Council on

COMMUNITY SERVICE AND EDUCATION

Assembly Hall 2 — 9:00 A.M. to 12:00 Noon

Chairman
OGLESBY PAUL, *Chicago, Ill.*

Co-Chairman
SIDNEY SCHERLIS, *Baltimore, Md.*

Symposium:

NONDIETARY FACTORS IN CORONARY ARTERY DISEASE

9:00 A.M. to 11:00 A.M.

Participants:

I. T. T. HIGGINS, *Glamorgan, Wales*
ANCEL KEYS, *Minneapolis, Minn.*
JEREMIAH STAMLER, *Chicago, Ill.*
THOMAS R. DAWBER, *Framingham, Mass.*
CAROLINE B. THOMAS, *Baltimore, Md.*

11:00 INTERMISSION

11:15 BODY WEIGHT, BLOOD PRESSURE AND CHOLESTEROL IN WHITES AND NEGROES AND THE PROBLEM OF RACIAL PATTERNS OF CORONARY HEART DISEASE.

JEREMIAH STAMLER, HOWARD A. LINDBERG, DAVID M. BERKSON, WILDA MILLER, MARVIN TEMPLETON, and YOLANDA HALL, *Chicago, Ill.*

11:30 DEATH RATES AMONG PHYSICALLY ACTIVE AND SEDENTARY EMPLOYEES OF THE RAILROAD INDUSTRY.

HENRY L. TAYLOR, *Minneapolis, Minn.*, ERNEST KLEPETAR, *St. Paul, Minn.*, ANCEL KEYS, *Minneapolis, Minn.*, WILLIS PARLIN, *St. Paul, Minn.*, HENRY BLACKBURN, and THOMAS C. PUCHNER, *Minneapolis, Minn.*

11:45 ARE PRESENT DAY PRACTICES IN RECOMMENDING WORK FOR PERSONS WITH HEART DISEASE CORRECT?

WILLIAM B. TUTTLE and W. LEIGH COOK, *Pittsburgh, Pa.*

Morning Session on

CARDIOVASCULAR FILMS

Assembly Hall 3 — 9:30 A.M. to 12:30 P.M.

Moderator:
J. EDWIN FOSTER, *New York, N. Y.*

9:30 PHYSIOPATHOLOGY OF HYPERTENSION. (Color, Sound, 1958)

Author: C. HEYMANS, *Ghent, Belgium;* Producer: NORMAN P. SCHENKER, *Munich, Germany;* Sponsor: PFIZER LTD., *England*

INTRODUCTION AND DISCUSSION:
HAROLD D. GREEN, *Winston-Salem, N. C.*

10:10 DIRECT STUDIES OF THE ELECTRICAL ACTIVITY OF THE SPECIALIZED CONDUCTING SYSTEM OF THE HEART. (Color, Sound, 1960)

Authors and Producers: J. H. STUCKEY and B. F. HOFFMAN, *Brooklyn, N. Y.*

INTRODUCTION AND DISCUSSION:
J. H. STUCKEY, *Brooklyn, N. Y.*

10:40 BUFFERING OF CO_2 DURING HYPERCAPNIA. (Color, Sound, 1959)

Author: GABRIEL G. NAHAS, *New York, N. Y.;* Producer: HAROLD DIXON, *Walter Reed Army Institute of Research, Washington, D. C.;* Sponsor: WALTER REED ARMY INSTITUTE OF RESEARCH

INTRODUCTION AND DISCUSSION:
GABRIEL G. NAHAS, *New York, N. Y.*

11:15 INDUCED FIBRILLATORY ARREST IN OPEN-HEART SURGERY. (Color, Sound, 1960)

Author, Producer and Sponsor: WILLIAM W. L. GLENN, *New Haven, Conn.*

INTRODUCTION AND DISCUSSION:
WILLIAM W. L. GLENN, *New Haven, Conn.*

12:00 DAMAGES OF "SILICONE-LIKE PROPERTY" OF VASCULAR ENDOTHELIUM BY ARTERIOSCLEROGENIC SUBSTANCES AND THEIR PREVENTION BY NIALAMIDE. (Color, Sound, 1960)

Author and Producer: TAKIO SHIMAMOTO, *Tokyo, Japan*

INTRODUCTION AND DISCUSSION:
TAKIO SHIMAMOTO, *Tokyo, Japan*

SUNDAY AFTERNOON
OCTOBER 23, 1960

Sixth Session on

CLINICAL CARDIOLOGY

Arranged by the COUNCIL ON CLINICAL CARDIOLOGY *and the* COUNCIL ON COMMUNITY SERVICE AND EDUCATION

Opera House — 2:00 P.M. to 5:00 P.M.

Chairman
HERBERT POLLACK, *New York, N. Y.*

Co-Chairman
R. BRUCE LOGUE, *Atlanta, Ga.*

Symposium:

LIPIDS AND ARTERIOSCLEROSIS

2:00 P.M. to 3:30 P.M.

2:00 OUTLINE OF THE BASIC PROBLEM.
HERBERT POLLACK, *New York, N. Y.*

2:15 RELATIONSHIP OF DIET TO SERUM CHOLESTEROL.
ROBERT E. OLSON, *Pittsburgh, Pa.*, and LAURANCE W. KINSELL, *Oakland, Calif.*

2:35 RELATIONSHIP OF SERUM CHOLESTEROL TO ATHEROGENESIS.
ROBERT M. O'NEAL, *St. Louis, Mo.*

2:50 DIETARY FACTORS OTHER THAN FATS THAT INFLUENCE BLOOD CHOLESTEROL.
ANCEL KEYS, *Minneapolis, Minn.*

3:00 NECESSITY FOR STANDARDIZATION OF SERUM CHOLESTEROL DETERMINATIONS.
GEORGE MANN, *Nashville, Tenn.*

3:10 DISCUSSION

3:30 INTERMISSION

3:45 SIDE EFFECTS OF NICOTINIC ACID IN TREATMENT OF HYPERCHOLESTEROLEMIA.
KENNETH G. BERGE, RICHARD W. P. ACHOR, NORMAN A. CHRISTENSEN, HAROLD L. MASON, and NELSON W. BARKER, *Rochester, Minn.*

4:00 FATE OF A PATIENT WITH SO-CALLED "MILD CORONARY."
WILLIAM LIKOFF, LEONARD DREIFUS, and SHELDON R. BENDER, *Philadelphia, Pa.*

4:15 INCIDENCE OF CORONARY-ARTERY DISEASE AT NECROPSY IN A COMMUNITY OF 30,000.
RALPH E. SPIEKERMAN, JOHN T. BRANDENBURG, RICHARD W. P. ACHOR, and JESSE E. EDWARDS, *Rochester, Minn.*

4:30 COLLATERAL ARTERIAL CHANNELS IN THE LIVING HUMAN WITH CORONARY ARTERY DISEASE.
F. MASON SONES, JR., and EARL K. SHIREY, *Cleveland, Ohio*

4:45 LONG-TERM ANTICOAGULANT THERAPY AFTER ACUTE MYOCARDIAL INFARCTION.
PAUL R. KUHN, *Chicago, Ill.*, ALBERT L. VAN NESS, *Bloomington, Ill.*, RICHARD J. JONES, and BARBARA S. HELMSTETTER, *Chicago, Ill.*

SIMULTANEOUS SCIENTIFIC SESSIONS

Council on

BASIC SCIENCE (II)

Assembly Hall 1 — 2:00 P.M. to 5:00 P.M.

Chairman
GORDON K. MOE, *Utica, N. Y.*

Co-Chairman
MANFRED L. KARNOVSKY, *Boston, Mass.*

2:00 DO LYMPHATIC VESSELS EXIST IN THE HEART VALVES OF THE DOG?
ALBERT J. MILLER, RUTH PICK, and LOUIS N. KATZ, *Chicago, Ill.*

2:15 CITRIC ACID METABOLISM IN CARDIAC MITOCHONDRIA.
MENARD M. GERTLER, *New York, N. Y.*

2:30 IMPORTANCE OF FREE FATTY ACID AS ENERGY SOURCE FOR MYOCARDIUM IN PERFUSED RAT HEART.
JOSEPH C. SHIPP, *Gainesville, Fla.* and LIONEL OPIE, *Boston, Mass.*

2:45 PERMEATION OF ANIONIC METABOLITES INTO MUSCLE.
ERNEST C. FOULKES and C. M. PAINE, *Cincinnati, Ohio*

3:00 RESPONSES IN ABDOMINAL MUSCLES ELICITED BY SUDDEN CHANGES IN CENTRAL BLOOD VOLUME.
WILLIAM B. YOUMANS, LARRY D. DAVIS, DOROTHY I. BRIGGS, and KENNETH L. GOETZ, *Madison, Wis.*

3:15 HEMODYNAMIC OBSERVATIONS ON THE FUNCTION OF THE LEFT ATRIUM IN MAN.
EUGENE BRAUNWALD, CHARLES J. FRAHM, and JOHN ROSS, JR., *Bethesda, Md.*

3:30 INTERMISSION

3:45 SIGNIFICANCE OF ACTIVE ION TRANSPORT ACROSS LARGE BLOOD VESSEL WALLS.
PHILIP N. SAWYER, IGNATIUS VALMONT, *Brooklyn, N. Y.*, DAVID W. HARSHAW, *Philadelphia, Pa.*, HAROLD STEINBAUM, and JOEL LEVINE, *Brooklyn, N. Y.*

4:00 ROLE OF CAROTID AND INTRACARDIAC BARORECEPTORS AND OF VASOACTIVE DRUGS IN THE CONTROL OF THE VENOUS BED.
CHARLES J. FRAHM, JOHN ROSS, JR., and EUGENE BRAUNWALD, *Bethesda, Md.*

4:15 STUDY OF LUNG COMPLIANCE AND SURFACE TENSION IN PULMONARY EDEMA.
RICHARD A. OBENOUR, HERBERT A. SALTZMAN, and HERBERT O. SIEKER, *Durham, N. C.*

4:30 FIBRIN INTERMEDIATES AS INDICATORS OF THROMBIN ACTIVITY IN VIVO.
JOHN R. SHAINOFF and IRVINE H. PAGE, *Cleveland, Ohio*

4:45 CARDIODYNAMIC EFFECTS OF EXPERIMENTAL BUNDLE-BRANCH BLOCK IN THE DOG.
JAMES R. WENNEMARK, DAVID F. BLAKE, and PAUL KEZDI, *Chicago, Ill.*

Council on

CARDIOVASCULAR SURGERY (II)

Assembly Hall 2 — 2:00 P.M. to 5:00 P.M.

Chairman
HENRY SWAN, *Denver, Colo.*

Symposium:

HYPOTHERMIA AND EXTRACORPOREAL CIRCULATION

2:00 P.M. to 3:30 P.M.

2:00 PHYSIOLOGY OF HYPOTHERMIA.
WILFRED G. BIGELOW, *Toronto, Canada*

2:20 METHOD OF HYPOTHERMIA.
WILFRED G. SEALY, *Durham, N. C.*

2:40 EXTRACORPOREAL CIRCULATION AND HYPOTHERMIA.
FRANK GERBODE, *San Francisco, Calif.*

3:00 AUTOGENOUS OXYGENATION AND PROFOUND HYPOTHERMIA.
F. JOHN LEWIS, *Chicago, Ill.*

3:20 DISCUSSION

3:30 INTERMISSION

3:45 CLINICAL RESULTS WITH THE USE OF A CONTINUOUSLY MONITORED EXTRACORPOREAL CIRCULATION.
BRUCE C. PATON and HENRY SWAN, *Denver, Colo.*

4:00 ANAEROBIC METABOLISM AND METABOLIC ACIDOSIS DURING CARDIOPULMONARY BYPASS.
WALTER F. BALLINGER, II, HEINZ VOLLENWEIDER, LOUIS PIERUCCI, JR., and JOHN Y. TEMPLETON, III, *Philadelphia, Pa.*

4:15 MYOCARDIAL METABOLISM IN SELECTIVE EXTREME HYPOTHERMIA OF THE HEART.
MAURICE ADAM, IVAN E. DANHOF, BEN F. MITCHEL, and MILTON V. DAVIS, *Dallas, Texas*

4:30 OBSERVATIONS ON LEFT VENTRICULAR PRESSURE AND EJECTION DYNAMICS IN HYPOTHERMIA.
WALTER L. FLOYD, MARCUS L. DILLON, *Durham, N. C.*, and ARNOLD M. WEISSLER, *Galveston, Texas*

4:45 DIRECT STUDIES OF THE SPECIALIZED CONDUCTING SYSTEM DURING HYPOTHERMIA.
JACKSON H. STUCKEY, BRIAN F. HOFFMAN, ALBIN A. BAGDONAS, JUAN PIERA, and ROBERT S. VENEROSE, *Brooklyn, N. Y.*

AFTERNOON SESSION ON CARDIOVASCULAR FILMS

Assembly Hall 3 — 2:00 P.M. to 4:45 P.M.

Moderator:
J. EDWIN FOSTER, *New York, N. Y.*

2:00 CREATION OF PULMONIC VALVULAR STENOSIS USING BYPASS PROCEDURE. (Color, Sound, 1960)

Authors: YOUSIF D. AL-NAAMAN, WILLIAM M. ROGERS, JAMES S. HARRISON, and ALI K. MAKSAD, *New York, N. Y.*; Producer: LEWIS KOSTER, *New York, N. Y.*; Sponsor: NEW YORK HEART ASSOCIATION, *New York, N. Y.*

INTRODUCTION AND DISCUSSION:
WILLIAM M. ROGERS, *New York, N. Y.*

2:15 DIAGNOSIS OF COMMON CONGENITAL CARDIAC ANOMALIES. (Color, Sound, 1960)

Author and Producer: JACK M. MARTT, *Columbia, Mo.*; Sponsor: DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY OF MISSOURI, *Columbia, Mo.*

INTRODUCTION AND DISCUSSION:
JACK M. MARTT, *Columbia, Mo.*

2:45 SURGICAL TREATMENT OF RENOVASCULAR HYPERTENSION. (Color, Sound, 1960)

Authors: GEORGE C. MORRIS, JR., E. STANLEY CRAWFORD, DENTON A. COOLEY, and MICHAEL E. DE BAKEY, *Houston, Texas*

INTRODUCTION AND DISCUSSION:
MICHAEL E. DE BAKEY, *Houston, Texas*

3:20 SURGICAL TREATMENT OF AORTIC VALVULAR DISEASE WITH ARTIFICIAL VALVES. (Color, Sound, 1960)

Author and Sponsor: EARLE B. KAY, *Cleveland, Ohio*; Producer: ST. VINCENT CHARITY HOSPITAL, *Cleveland, Ohio*

INTRODUCTION AND DISCUSSION:
EARLE B. KAY, *Cleveland, Ohio*

4:10 DIAGNOSIS OF VENTRICULAR SEPTAL DEFECTS. (Color, Sound, 1960)

Authors: J. H. KAY, R. M. ANDERSON, S. BERNSTEIN, E. F. DUNNE, O. MAGIDSON, J. E. MEIHAUS, and P. C. DYKSTRA, *Los Angeles, Calif.*; Producer: PAT DOWLING PICTURES, *Los Angeles, Calif.*; Sponsor: UPJOHN, *Kalamazoo, Mich.*

INTRODUCTION AND DISCUSSION:
J. H. KAY, *Los Angeles, Calif.*

Council on

COMMUNITY SERVICE AND EDUCATION

Jointly with

AMERICAN DENTAL ASSOCIATION

Assembly Hall 3 — Friday, October 21, 1960
2:00 P.M. to 5:00 P.M.

Chairman
FRANCIS L. CHAMBERLAIN, *San Francisco, Calif.*

Co-Chairman
J. PAUL GUIDRY, *Kirkwood, Mo.*

Symposium:

MANAGEMENT OF MEDICAL-DENTAL PROBLEMS IN PATIENTS WITH CARDIOVASCULAR DISEASES

2:00 INTRODUCTORY REMARKS.

2:15 NATURE OF RESTORATIVE, PERIODONTAL AND ORAL SURGICAL DENTAL SERVICES.
ROY W. OSTERKAMP, *St. Louis, Mo.*

2:30 INCIDENCE OF TRANSIENT BACTEREMIAS FOLLOWING DENTAL MANIPULATIVE PROCEDURES.
I. B. BENDER, *Philadelphia, Pa.*

2:45 PROPHYLACTIC USE OF ANTIBIOTICS IN PATIENTS WHO REQUIRE DENTAL MANIPULATIVE PROCEDURES.
ROBERT S. PRESSMAN, *Philadelphia, Pa.*

3:00 INTERMISSION

USE OF VASOCONSTRICTING AGENTS IN LOCAL ANESTHETICS. CONSIDERATION OF PATIENTS RECEIVING ANTICOAGULANT, ANTIHYPERTENSIVE AND DIURETIC DRUGS:

3:20 DENTAL CONSIDERATIONS.
BRUNO KWAPIS, *St. Louis, Mo.*

3:40 PHARMACOLOGIC CONSIDERATIONS.
STANLEY C. HARRIS, *Chicago, Ill.*

4:00 MEDICAL CONSIDERATIONS.
FRANCIS L. CHAMBERLAIN, *San Francisco, Calif.*

4:30 DISCUSSION

Council on

COMMUNITY SERVICE AND EDUCATION

SESSION FOR NURSES

Assembly Hall 3 — Saturday, October 22, 19[illegible]

Morning Session 9:30 A.M. — 12:00 Noon

Chairman
FLORENCE GIPE, *Baltimore, Md.*

Symposium:

TOTAL CARE OF THE PATIENT WITH MYOCARDIAL INFARCTION

Moderator:
SISTER AGNITA CLAIRE, *St. Louis, Mo.*

9:30 INTRODUCTORY REMARKS.

9:40 A PATIENT'S EXPERIENCES.
JOSEPH I. GILKISON, *Dallas, Texas.*

10:00 MEDICAL CARE.
ROBERT SINGLETON, *Baltimore, Md.*

10:20 NURSING CARE DURING HOSPITALIZATION AND REHABILITATION.
MILDRED CRAWLEY, *Bethesda, Md.*

10:40 SOCIAL ASPECTS.
ETHER SMITH, *Oklahoma City, Okla.*

11:00 NUTRITIONAL ASPECTS.
JEAN HANKIN, *Providence, R. I.*

11:20 INTERMISSION

11:30 DISCUSSION

Afternoon Session 2:00 P.M. — 5:00 P.M.

Chairman
MYRTLE H. COE, *Minneapolis, Minn.*

Panel:

NURSING PATIENTS WITH CARDIOVASCULAR DISEASES:

Discussion of Problems Presented by the Audience.

Participants:

SISTER AGNITA CLAIRE, *St. Louis, Mo.*
MILDRED CRAWLEY, *Bethesda, Md.*
JOSEPH I. GILKISON, *Dallas, Texas*
FLORENCE GIPE, *Baltimore, Md.*
MARY GREGORY, *St. Louis, Mo.*
JEAN HANKIN, *Providence, R. I.*
ROBERT SINGLETON, *Baltimore, Md.*
ETHER SMITH, *Oklahoma City, Okla.*

ABSTRACTS OF LECTURES

GEORGE E. BROWN MEMORIAL LECTURE

Clinical Physiology of the Splanchnic Circulation

Stanley E. Bradley, M.D.

The splanchnic vasculature is unique in possessing a complex arrangement of resistances, both in series and in parallel, which embrace a voluminous venous system. The structural organization of the bed is admirably suited to its function as an adjustable reservoir of blood and, at the same time, its operation as an independent variable resistance. Splanchnic blood flow can be estimated in man on the Fick principle from the rate at which infused sulfobromophthalein sodium (BSP) is removed from the blood at equilibrium and from the simultaneous arterial-hepatic venous concentration difference. The volume of blood within the bed may be determined on the basis of the regional dilution of radioactive iodine labeled human serum albumin. Anatomic data support the view that the bulk of the splanchnic blood volume lies within well-muscled veins and that changes in volume may be ascribed in part to venomotor activity. The normal parameters of splanchnic blood flow and volume, determined in a large series of normal human subjects, indicate that approximately 25 per cent of the cardiac output passes through the splanchnic bed each minute and that some 20 per cent of the total blood volume is contained within it. Blood flow appears to be determined by the interaction of local requirements and the demands of the cardiovascular system as a whole. Thus splanchnic vasodilatation occurs shortly after moderate blood loss, presumably because tissue need is able to overcome an opposing tendency to vasoconstriction. Splanchnic blood volume may change independently of flow, increasing, for example, when flow decreases following administration of hexamethonium or when flow rises after Apresoline. In general, shifts in splanchnic volume appear to be secondary in nature, the direction and extent of change depending upon the relative importance of many simultaneous influences, including central venous pressure, vasomotor activity, and intra-abdominal pressure. The clinical implications of these considerations will be discussed with special reference to the problems of arterial pressure regulation and congestive heart failure.

LEWIS A. CONNER MEMORIAL LECTURE

Physiology of Circulation as Viewed by the Internist

Eugene A. Stead, Jr., M.D.

The peripheral arteries change little in volume with each systole. The volume change so characteristically noted by the physician when he feels the radial artery is produced by the physician. He applies enough pressure to collapse the vessel in diastole and feels the expansion of the vessel caused by the systolic pressure wave. Petersen has shown that the change in vessel circumference under physiologic conditions does not exceed 5 per cent.

Under usual conditions, little energy is lost from the radial artery by viscous friction or by expansion of the arterial wall. The force from the systolic contraction of the ventricle largely expresses itself as a rise in pressure. When the systolic forward thrust stops, the pressure abruptly falls. This sudden decrease in pressure is associated with a reversal in gradient, the pressure in the radial artery now exceeding that in the brachial artery for a variable period.

Because the system is tight, small changes in the forms of energy present in the system will be expressed as large changes in pressure. A loss of energy from viscous friction from arterial obstruction markedly lowers the pulse pressure. In the absence of arterial obstruction, an equally great loss of energy by viscous friction can be achieved by opening the arterioles widely.

ABSTRACTS OF PAPERS

Abstracts are listed alphabetically by first author

**Established Investigator, American Heart Association, 1959-1960*
†Research Fellow, American Heart Association, 1959-1960

Precordial Electrocardiogram during Exercise

Ramon F. Abarquez, Alvin H. Freiman, Frederic Reichel, and John S. LaDue, New York, N. Y.

The precordial electrocardiogram, continuously monitored in subjects performing the 2-step test, was rendered free of muscle interference and baseline shift by employing cupped wire mesh electrodes, bentonite electrode paste, and a new system of electrode placement. The right arm electrode was placed on the right ear lobe, the left arm electrode over the ensiform process, and the left leg electrode at V_7 position. Unipolar leads comparable to the standard precordial leads were recorded simultaneously on a 4-channel electrocardiograph.

Preliminary findings show that in 135 of 150 instances, the maximum electrocardiographic changes occurred before the termination of exercise and started to revert toward control levels in 5 to 30 seconds after termination of exercise. V_3 and V_5 leads showed best the changes occurring during exercise. In 60 normal subjects, 48 had a sinus rate of 110 to 150/min. with S-T segment depressions of 1 mm. in 46 instances and 1.5 mm. in 5 cases. Three subjects with S-T segment depressions of 2 mm., 3 mm., and 3.5 mm. had sinus tachycardia of 175/min. T waves inverted in 2 subjects.

In 4 patients with coronary artery disease, ischemic changes were present during exercise, but the 1-minute postexercise tracings were equivocal. One patient showed ischemic changes 13 seconds after the onset of exercise so that the extension of the test beyond this point would be unnecessary. The occurrence of ischemic changes with or without arrhythmia preceding angina were also noted.

Myocardial Metabolism in Selective Extreme Hypothermia of the Heart

Maurice Adam, Ivan E. Danhof, Ben F. Mitchel and Milton V. Davis, Dallas, Texas

Although prolonged exposure of the heart for surgical purposes is often desired, it usually requires sacrificing myocardial efficiency during the immediate postperfusion period. Metabolic changes underlying this decreased efficiency must be better understood in order to minimize these undesirable changes. Mongrel dogs were subjected to total cardiopulmonary bypass, systemically normothermic, while the coronary arteries were perfused with oxygenated blood at varying temperatures, using a Brown-Harrison heat exchanger. Myocardial and blood specimens from both the general circulation and coronary sinus were removed at normal temperatures, early and again later during extreme hypothermia (in some cases after an additional period without perfusion), and also after rewarming had been completed. Myocardial glycogen, potassium, sodium, and intracellular water were estimated, as well as the potassium, pH, plasma hemoglobin, and glucose levels of the perfusate and coronary sinus blood. After the initial 5 minutes of cooling (heart temperature approximately 10 C.), there were increases in myocardial glycogen, potassium, and intracellular water. An additional 20 minutes of zero coronary perfusion at about 10 C. did not change these parameters significantly and was generally reversible upon the reinstitution of adequate perfusion and rewarming. Myocardial hypothermia was generally accompanied by fibrillation. Although only the heart was cooled, the systemic potassium decreased in a manner similar to that observed in total body hypothermia.

SELECTION OF PAPERS: Abstracts of papers and exhibits submitted were evaluated by the Program Committee of the appropriate council or the Subcommittee on Exhibits. The final selections were made by the Committee on Scientific Sessions Program of the American Heart Association on the recommendations of the Council Program Committees.

The data indicate that the metabolic substrate of ıe myocardium changes rapidly with cooling, as ıdicated by the increases in myocardial glycogen ıd potassium. The uptake of glucose by the ıyocardium continued throughout the hypothermic eriod, but at a decreased rate at the lower temeratures. Since fibrillation accompanied the inease of myocardial glycogen, it is concluded that ıe mechanism previously described in preventing brillation by administration of intravenous gluse during hypothermia was different from the ıechanism underlying the deposition of glucose ithin the myocardium.

)bservations on the Mechanism of the Wolff-Parkinson-White Syndrome

William B. Adamson and Donald G. Strole, Abilene, Texas

This syndrome, first described in detail by Wolff, Parkinson, and White can perhaps best be described as an electrocardiographic pattern, characterized by a shortening of the A-V conduction time with a compensatory lengthening of the I-V conduction time, with slurring of the initial segment of the QRS producing the "Delta" wave. Numerous variations of this typical pattern occur. Many cases are apparently of congenital origin, but not infrequently such patterns appear during the course of organic heart disease. Records of approximately 100 such cases have been studied, and evidence is presented which seems to indicate that the pacemaker is an irritable ectopic atrial focus. The occurrence of frequent atrial premature beats conforming to rather typical Wolff-Parkinson-White configuration is significant. This hypothesis does not preclude a functioning atrioventricular fasciculus (bundle of Kent), nor does it depend on the functional activity of this structure.

Carcass Electrolytes in Dogs with Heart Failure

Robert J. Adolph, Seattle, Wash., and Harry A. Bliss, Chicago, Ill.

Chronic congestive heart failure with ascites was ıduced in 4 dogs by surgical production of tricusid insufficiency and pulmonary stenosis. These ıimals and 4 normal dogs of similar weight were ıcrificed 9 minutes after acetyl strophanthidin, dministered to determine its effect on heart muscle ı studies not reported here. Ascitic fluid was moved and is not included in the data summaıed below. The entire carcasses, shorn of most air, were then homogenized after passage through rinders with increasingly fine mesh. Two samples om each carcass homogenate were analyzed for ater, fat, nitrogen, sodium, potassium, and chloride. Results are expressed as mEq./Kg. wet fat-free tissue unless otherwise noted.

Animals with heart failure showed significantly ($p < .01$) more sodium (69.62, S.D. 6.23) and chloride (38.82, S.D. 1.01) than controls, in which sodium was 57.95, S.D. 4.72 and chloride 32.87, S.D. 4.59. In dogs with failure, potassium (51.64, S.D. 4.06) was similar to control values (51.63, S.D. 5.69).

Nitrogen, as Gm./Kg. fat-free solids, was almost the same (115.2, S.D. 4.0) in animals with heart failure as in controls (117.3, S.D. 2.8). In animals with failure, water determinations (743.4, S.D. 15.6 Gm./Kg. wet fat-free tissue) were comparable to control values (732.1, S.D. 13.7). The potassium : nitrogen ratio was slightly, but not significantly higher (1.740, S.D. 0.14 mEq. K/Gm. N) in dogs with failure than in controls (1.646, S.D. 0.19). Thus, contrary to some previous evidence, potassium deficiency and increased tissue hydration, except for ascites, did not appear in heart failure. The location of the excess sodium and chloride in animals with failure is not apparent from these data.

"Iatrogenic" Aorticocardiac Fistula Following Open Heart Surgery

Magnus H. Agustsson, Egbert H. Fell, Benjamin M. Gasul, Milton Weinberg, Jr., and Zwi Steiger, Chicago, Ill.

During the last 2 years we have encountered 3 patients who developed aorticocardiac fistulas following "successful" corrective surgery, for tetralogy of Fallot in 2 cases, and for ventricular septal defect in 1 case. The clinical picture in these 3 patients was characterized by the appearance of a loud continuous murmur over the lower precordial area, well demonstrated in the phonocardiogram. In 2 patients, congestive heart failure appeared shortly after surgery and progressed to an intractable failure in 1 to 2 months, accompanied by massive anasarca, hydrothorax and ascites. The third patient remained asymptomatic. Retrograde aortograms performed 2 or more months postoperatively demonstrated the aorticocardiac fistulas in each case. In case 1 and case 2, the fistulas arose from the right coronary sinus and communicated with the right ventricle; in case 3, a perforated right coronary cusp produced severe aortic regurgitation. Case 1 and case 3 who developed severe heart failure were successfully reoperated with the aid of a cardiopulmonary bypass procedure. The heart failure promptly disappeared following repair of the fistulas.

In spite of the close proximity of the pulmonary conus to the aortic sinuses, postoperative rupture of these sinuses has not been reported. It is probable that some of these cases are undiagnosed

clinically. According to Drs. Edwards and Lev, with whom we discussed these patients, the diagnosis may be missed even at necropsy, particularly since the pulmonary conus becomes deformed following corrective surgery. The diagnosis of this surgically induced and surgically remediable complication is of utmost importance since, if not corrected, it may result in death.

Comparison of Three Oral Penicillins for Antistreptococcal Prophylaxis

Chloe G. Alexson, Margaret L. Rathbun, and James A. Manning, Rochester, N. Y.

This study reports a comparison of buffered potassium penicillin G, benzathine penicillin G, and phenoxymethyl penicillin given as a single 200,000 unit daily tablet as antistreptococcal agents in a closely controlled community rheumatic fever prophylaxis program.

During the initial 30 months of study, 470 patients were observed for a total of 7,179 monthly visits. Selection of agent was random and the 3 groups were similar in descriptive characteristics. Fifty per cent of the entire group was composed of children under the age of 20 years. Patients were evaluated monthly by interview, routine throat culture and ASO antibody determination.

Monthly attendance was 90 per cent. The streptococcal attack rate (positive culture and/or significant increase in ASO antibody titer) was 10 per cent per patient year for the potassium penicillin G group. It was 9.8 per cent per patient year for benzathine penicillin G, and 6.4 per cent per patient year for the phenoxymethyl penicillin group. These differences were not statistically significant.

The over-all streptococcal attack rate was 8.7 per cent per patient year. Of this, the over-all positive culture rate was 0.7 per cent per patient year and was not significantly different in the 3 groups. The over-all rheumatic fever recurrence rate was 0.3 per cent per patient year and was again not significantly different in the 3 agent groups.

These data indicate that the 3 oral penicillins tested are equally effective in streptococcal prophylaxis. They also indicate that a closely controlled community oral prophylaxis program can maintain adequate antistreptococcal and antirheumatic fever prophylaxis.

Correlation of Electrocardiograms and Vectorcardiograms with Autopsies

Bertram J. Allenstein, Beverly Hills, Calif., and Clifford S. Reusch, Duarte, Calif.

The hearts of 128 patients who had both routine 14-lead electrocardiograms and direct spatial vectorcardiograms with at least 2 systems were studied at post mortem. Currently accepted standards for cardiac weights and measurements were used. The material was analyzed in the following groupings: right ventricular hypertrophy, left ventricular hypertrophy, combined right and left ventricular hypertrophy, myocardial infarction, no myocardial infarction or hypertrophy. Each group was correlated with the electrocardiogram and vectorcardiogram to evaluate the diagnostic accuracy of each.

Positive correlation for both electrocardiograms and vectorcardiograms was excellent with right ventricular hypertrophy and poor with combined ventricular hypertrophy and with myocardial infarction coexistent with left ventricular hypertrophy. The vectorcardiogram had considerably better correlation than the electrocardiogram with combined hypertrophy, and moderately better correlation with right ventricular hypertrophy and left ventricular hypertrophy. For the total group, there was greater correlation with the vectorcardiogram and postmortem study.

The validity of cardiac weights and measures in relation to electrophysiologic phenomena is discussed in relation to the correlation obtained and proposals made to increase the accuracy of electrocardiographic and vectorcardiographic interpretation.

Congenital Heart Disease in Five Members of One Family

Bertram J. Allenstein, Beverly Hills, Calif., and Max H. Weil, Los Angeles, Calif.

The role of genetic factors in congenital heart disease has not been clearly established. Review of recent studies on a total of 1,565 patients with congenital heart lesions indicated an incidence of less than 2 per cent among siblings of the propositi. However, the occurrence of congenital heart disease in 5 members of 1 family, consisting of the parents and 10 children, with an interatrial septal defect of the secundum type in each affected member, indicates the great likelihood of genetic transmission. Previously, the defects in 4 members were reported.

Diagnosis was made by cardiac catheterization and confirmed at surgery in the father, 43, and 1 son, 8. Another son, 13, and a daughter, 16, also had cardiac catheterization and diagnosis was confirmed at autopsy. In the fifth patient, a daughter, aged 2, diagnosis was made at cardiac catheterization. In addition to the interatrial defect, the son, aged 13, had a tetralogy of Fallot (pentalogy). The daughter, aged 16, had a concomitant ventricular septal defect. Both the 8-year-old son and 2-year-old daughter had infundibular pulmonic stenosis, in addition.

The occurrence of interatrial septal defects in 3 members of 1 family has been reported, but no larger familial incidence of this defect diagnosed by other than clinical means has been reported. No other reports were found in which definitive diagnosis of congenital heart disease was made in 5 members of 1 family.

Interrelation of Coronary Occlusion, Intercoronary Anastomosis, Myocardial Infarction, and Angina Pectoris

Robert B. Allison, Felix L. Rodriguez, Walter H. Abelmann, and Laurence B. Ellis, Boston, Mass.*

An unselected series of 250 hearts was studied at the Boston City Hospital by a modified Schlesinger's coronary injection technic combined with meticulous exploration of the myocardium. Independently, the clinical records were reviewed for clinical evidence of coronary artery disease.

The average age was 68.1 years. There were 138 men and 112 women, 210 white people and 40 Negroes. Fifty-seven of 58 hearts with 1 or more major coronary occlusions showed intercoronary anastomoses, which were found in only 13 per cent (2 of 15) of normal hearts. Blumgart's contention that intercoronary anastomoses can completely protect the myocardium from infarction, although disputed by others, was confirmed. Ten isolated coronary artery occlusions without myocardial infarction were found, and in each extensive intercoronary anastomoses existed.

Seventy-two (29 per cent) of the hearts showed 115 myocardial infarcts. Twenty-one per cent of these infarcts were not associated with coronary occlusions and were characterized as a group by being small, healed, not accompanied by angina, and clinically not evident.

Twenty-five of 27 angina patients had coronary occlusions or myocardial infarcts or both. The number of occlusions per heart in patients with occlusions, with or without angina, did not differ.

False positive clinical diagnosis of definite myocardial infarction was uncommon (4 of 29, or 14 per cent) but 40 per cent (29 of 72) of pathologic myocardial infarctions were clinically not diagnosed. When the clinical diagnosis of definite coronary artery disease was made, occlusion or severe stenosis of the coronary arteries was found at autopsy in 37 of 43 cases (86 per cent).

New Angiocardiographic Sign of Aortic Regurgitation: Its Utilization for the Measurement of Regurgitant Flow

Rene A. Arcilla, Magnus H. Agustsson, Zwi Steiger, and Benjamin M. Gasul, Chicago, Ill.

A modified technic of retrograde aortography was performed on 8 patients with, and on 5 patients without aortic insufficiency. The method consists of a rapid injection of a contrast substance (Hypaque 90 per cent) into the proximal portion of the descending aorta, using a large catheter introduced at the left brachial artery, and taking biplane radiographs at a speed of 8 pictures per second. The aortograms demonstrate the abnormal pulsatile flow in aortic insufficiency. During ventricular systole, the opacified column in the descending aorta moves distally, and during diastole it returns centripetally. The forward movement of the contrast substance is accompanied by immediate dilatation of the aorta, and the centripetal return by a marked reduction in the aortic diameter. These to-and-fro movements of the contrast substance and the marked difference in the aortic diameters during systole and diastole were not observed in the patients without aortic insufficiency.

The volume of the aortic segment traversed by the contrast substance in its forward movement is equivalent to the stroke volume that has bypassed the brachiocephalic vessels. Similarly, the volume of the aortic segment traversed during the following centripetal movement represents the regurgitant volume excluding that coming from the brachiocephalic vessels. The degree of regurgitation is expressed as a percentage of the stroke volume. Of the 8 patients with aortic insufficiency studied, the mean stroke volume was 45 ml./M^2 (range 35 to 55 ml.), the mean regurgitant volume was 30 ml./beat/M^2 (range 16 to 40 ml.), and the per cent regurgitation of the stroke volume ranged from 40 to 75 per cent.

Correlative Study of the Electrocardiogram and the Hemodynamics of 101 Patients with Left Ventricular Diastolic Overload

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Electrocardiograms of 101 patients with hemodynamic evidences of left ventricular diastolic overload were analyzed. Ventricular septal defect was present in 73 patients, patent ductus arteriosus in 25, and 3 patients had both anomalies. Twenty-three patients had pulmonary artery systolic pressures over 60 mm. Hg, and none of them had a right-to-left shunt. Biventricular hypertrophy was present in 28 tracings and left ventricular hypertrophy alone in 63. The T waves, QRS complexes and ventricular activation time were compared with normal mean values for the patient's age (± 1 S.D.), and the difference plotted against the degree of diastolic overload reflected by the ratio of the systemic flow (SBF) to pulmonary flow

(PBF). In patients with patent ductus arteriosus, the T waves were within normal limits in 11, abnormally tall in 9, and were of diminished amplitude in 5. In those with ventricular septal defect, they were within normal limits in 36, abnormally tall in 26, and were of diminished amplitude in 11. No correlation existed between the amplitude and configuration of the T waves and the degree of diastolic overload. In fact, the abnormally tall T waves were encountered mostly in patients with SBF/PBF ratio of 60 to 30 per cent, and the low amplitude waves in those with SBF/PBF ratio of 30 per cent or less. The voltage of $R_6 + S_1$ ($R_8 + S_2$) was abnormally high in 33 per cent of the tracings. Abnormally deep Q waves in the standard and left precordial leads were also noted in 32 per cent of our patients, especially in those with large left-to-right shunts. Our findings reveal no definite correlation between the electrocardiograms and hemodynamic findings in patients with varying degrees of left ventricular diastolic overload. The abnormal Q waves and QRS complexes are more informative than the T waves.

Regional Flow-Pressure Relationships in Response to Vasoactive Drugs in the Intact Dog and Sheep

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Using miniature electromagnetic flowmeters implanted around vessels, blood flow measurements were made simultaneously from the carotid, renal, femoral, internal iliac, and uterine arteries in intact pregnant and nonpregnant dogs and sheep. Arterial pressure was measured with a strain gage connected to a contralateral carotid or femoral artery. Vascular resistance in each region was calculated from the arterial pressure and the regional blood flow. The effects of intravenous administration of epinephrine, norepinephrine, angiotensin, acetylcholine, oxytocin, and ergonovine were studied.

It was found that for any given change in arterial pressure, the blood flow response may differ from one region of the body to another. For instance, a rise in pressure induced by angiotensin produces consistently a marked fall in renal blood flow but an increase in uterine, iliac, and femoral flows and a little change in carotid flow. If the same pressure rise is induced by norepinephrine or epinephrine, the uterine and femoral flows decrease markedly while the renal and carotid flows change only slightly. These varying responses in the regional blood flow are mediated through specific changes in regional vascular resistances. The direction of these changes depends on various physiologic factors among which are the nature of the stimulus, the magnitude of change and the function of the area supplied by a given vessel. These studies point out the fallacy of attempting to derive information regarding regional circulation from the behavior of the so-called total peripheral resistance as calculated from the pressure and cardiac output.

Transient Hypoventilation during Exercise in Obese Subjects

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While many obese individuals experience respiratory distress on such activities as climbing stairs, and a much smaller number have resting hypercapnia, the relative frequency of these problems is unknown. In the present study, 14 obese and 25 nonobese subjects underwent a 10-minute period of exercise on a treadmill at 1.7 mph and a 10 per cent grade. The following variables were recorded: heart rate, respiratory frequency, minute ventilation, mixed expired and end-tidal CO_2 and N_2 concentrations. Derived data included alveolar (end-tidal) and mixed expired respiratory quotient (RQ), CO_2 production and O_2 consumption, alveolar CO_2 tension (PA_{CO_2}), and steady-state breathing reserve (ventilation/maximum ventilatory capacity). Twenty-three of the 25 normal subjects maintained a breathing reserve of more than 70 per cent, whereas only 4 of the 14 obese subjects could do so. This encroachment of ventilation on the breathing reserve was most marked in the extremely obese subjects. Hypoventilation at the steady state as manifested by increased PA_{CO_2} was not observed in the obese subjects; however, lowest RQ in the unsteady state (considered to be an index of hypoventilation) was significantly lower in the obese subjects as a group, and 4 obese subjects had values below 2 standard deviations from the control group mean. Five subjects with a diminished ventilatory response to 5 per cent CO_2 (previous study) also showed a diminished ventilatory response to exercise. Thus, moderate exercise severely taxes the ventilatory system of obese individuals and may result in transient periods of hypoventilation.

Mechanics and Work of Breathing in Atrial Septal Defect

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Dyspnea is a common symptom in atrial septal defect, although its genesis is poorly understood. In an attempt to evaluate this problem, the mechanics and work of breathing were measured in 9 pa-

t ents with atrial septal defect and correlated with t e hemodynamic derangements. Three of 4 p tients who were dyspneic following standard s ep exercise manifested hyperventilation and had a reduced maximum breathing capacity. In 8 p tients with 2- to 4-fold increase in pulmonary b ood flow (PBF), effective pulmonary compliance w as 0.064 to 0.116 L./cm. H_2O (mean: 0.098), a s gnificant reduction from normal (range: 0.129 to 0 276; mean: 0.170). Compliance was normal in a patient with elevated pulmonary vascular re- s stance and normal PBF. Viscous resistance v aried directly with pulmonary "capillary" pres- s re, and in 6 patients was greater than normal. T otal inspiratory lung work, measured by integra- t on of pressure-volume loops, was twice normal. These alterations in the mechanics of breathing may account for the dyspnea commonly observed.

Congenital Familial Nodal Rhythm

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It is known that isolated cardiac arrhythmias often exist without demonstrable heart disease; however, familial cardiac arrhythmias are extremely rare. In each of 4 available papers we have reviewed, atrial fibrillation has predominated. This report concerns 9 descendants of a common ancestor, covering 3 generations, who have manifested nodal bradycardia since birth or early youth. Younger members are asymptomatic. Four who have entered the fourth decade of life have experienced paroxysmal atrial fibrillation. Two adult members have been extensively investigated. Each presented atrial fibrillation which reverted to nodal bradycardia with treatment. Rarely, sinus bradycardia was seen. Large doses of intravenous atropine sulfate failed to produce significant increments in cardiac rate. Despite demonstrable cardiomegaly, appropriate cardiac catheter studies revealed normal hemodynamics and pressures and no evidence of shunting. It is concluded that regulation of cardiac output in these individuals is dependent primarily on stroke volume. Cardiomegaly results from "physiologic adaptation."

Inheritance of this trait apparently depends upon a dominant autosomal gene with a high degree of penetrance. The appearance of rare sinus beats precludes the possibility of congenital absence of the sino-atrial node.

The development of paroxysmal atrial fibrillation in apparent association with the attainment of the fourth decade of life is unexplained.

It seems apparent that, like physical characteristics, unusual disturbances in cardiac rhythm have genetic mechanism of expression.

Effects of Low Oxygen Tension and of Ischemia on Cardiac Conduction

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Cardiac conduction during low oxygen tension and ischemia was studied in dogs by use of a technic developed in this laboratory in which electrodes are implanted in the heart at selected locations along the conducting system while on cardiopulmonary bypass. Hypoxia was produced in 3 dogs by using 50 and 100 per cent nitrogen in the oxygenator for 60 and 120 minutes, and ischemia was produced in 7 dogs by cross-clamping the ascending aorta for 15 to 60 minutes. In addition, a dog with chronically implanted electrodes was placed on a respirator with 100 per cent nitrogen for 5 minutes. Electrical activity at the electrodes was monitored on an oscilloscope and photographed on paper moving 200 mm./sec.

Results indicate that atrial and A-V nodal conduction were the most sensitive to ischemia, while the specialized conducting system, particularly the Purkinje system, was relatively resistant. Ischemia lasting 40 minutes abolished all electrical activity. Severe hypoxia of 120 minutes duration with arterial oxygen saturations as low as 4 per cent depressed atrial electrical activity; however, the conducting system distal to the A-V node was not markedly affected. Similar changes were observed when the dog with chronically implanted electrodes was subjected to anoxia. Ventricular fibrillation consistently occurred during ischemia and not during hypoxia. The difference observed between the effects of ischemia and hypoxia on the conducting system would suggest that during ischemia other factors, such as the accumulation of metabolites and changes in pH and electrolytes, may play a greater role than lack of oxygen.

Relief of Aortic Stenosis by Sculpturing of the Valve

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While aortic stenosis remains a formidable surgical lesion, the improvement in operative technic and results over the past 4 years have reached a high degree of proficiency.

In the presence of a murmur of aortic stenosis, the appearance of dyspnea, fatigue, angina pectoris, fluid retention or pulmonary edema are harbingers of a rather abrupt devolutionary clinical pattern. Such patients, whether suffering from congenital or acquired aortic stenosis, should be investigated as potential candidates for operation. Patients with electrocardiographic evidence of left ventricular hypertrophy or strain and an aortic

gradient of 40 mm. Hg or more should be operated upon.

During the past 4 years, 146 patients with aortic stenosis have been operated by the open method. The various technics of surgical correction of the lesion which were employed include hypothermia, retrograde coronary sinus perfusion with total cardiopulmonary bypass, elective cardiac arrest, autogenous lung preparation, antigrade coronary artery perfusion with low and high flows with total bypass, and the current technic of complete cardiopulmonary bypass, moderate hypothermia with high flow coronary artery perfusion. This latter method has been used for approximately a year in 50 instances, with the lowest operative mortality and best clinical results of any of the methods employed. Simultaneously, actual removal of fibrosis and calcification by curettage, rongeur and excision has consistently restored valve mobility and flexibility. Marked symptomatic improvement with comparable postoperative physiologic findings has been the rule. A report of the results of our experience with the open treatment of congenital and acquired aortic stenosis has been prepared.

Hypoxia and Fetal Cardiovascular Anomalies

Bernard Baird and Sherburne F. Cook, Berkeley, Calif.

Teratogenic effects of hypoxia on Swiss albino mice were studied by continuous or discontinuous exposure during pregnancy to oxygen-deficient environments ranging to 25,000 feet. Prebreeding adaptation, impregnation, gestation, parturition and postpartum nurture were studied during such exposure. Functional criteria for differentiating physiologic from pathognomonic phenomena were adduced.

No cardiovascular anomalies were observed among 391 progeny of sea level control mice. A total of 27 congenital malformations, including 25 fetal cardiovascular anomalies, were found among 17 of 157 dissected offspring of hypoxia-exposed mice. Cardiovascular anomalies included right aortic arch, interventricular septal defect, distally arising right subclavian artery, interatrial septal defect and a triadic syndrome consisting of patent ductus arteriosus, dilated atria and diffuse granulation of the myocardium.

Those mice exposed discontinuously (6 hrs./day) to a simulated altitude of 20,000 feet produced 99 young, among which 1 clubfoot and 12 malformations of the cardiovascular system were detected. Among the 13 survivors of the 44 neonates produced during discontinuous exposure to 21,500 feet, 1 cleft palate and 3 deformities of the heart or great vessels were recorded. No anomalies occurred among the 45 offspring of mice exposed continuously to a simulated altitude of 14,200 feet.

Disturbed organogenesis and other indications of deranged homeostasis in intra-uterine contents correlated directly with the duration and intensity of hypoxia.

Anaerobic Metabolism and Metabolic Acidosis during Cardiopulmonary Bypass

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A rise in blood lactate during operations employing cardiopulmonary bypass has been described. However, it has been well established that elevations in lactate may occur in the absence of anaerobic metabolism. "Excess lactate" may be calculated and includes only that lactate formed as a result of anaerobic metabolism.

Six patients were studied before, during, and following intracardiac operations using a pump oxygenator of the Gibbon type. The cardiac defects consisted of 1 ventricular aneurysm, 2 atrial septal defects, and 3 acquired valvular lesions. In 3 patients, hypothermia was induced.

Blood samples were obtained from the femoral artery immediately following induction of anesthesia, following thoracotomy, at intervals during and after the cardiopulmonary bypass, and following closure of the chest. A blood sample was also obtained from the arterial line of the heart-lung machine prior to bypass. The following determinations were made: pH, oxygen content and capacity, carbon dioxide content, lactate, and pyruvate. All studies were performed on whole blood. The following calculations were made: p_{CO_2}, oxygen saturation, excess lactate, and the change in fixed acids.

In all cases, excess lactate was elevated in the blood sample from the heart-lung machine before bypass. However, this excess lactate was rapidly removed by the patient during the perfusion. Partial obstruction of the venae cavae before perfusion, inadequate flow rates, and arrhythmias all contributed to a rise in excess lactate and the fall depended on the rapidity of correction of these difficulties. A rise in excess lactate occurs during cooling and is probably related to slower cooling of the body muscle. The accumulation of lactate and pyruvate does not follow the same pattern as the accumulation of excess lactate, but does account for at least 70 per cent of the rise in fixed acids in all patients studied.

Comparison by Gas Chromatography of the Fatty Acid Content of Adipose Tissue with Dietary Intake of Fat in Vegetarian and Nonvegetarian Males

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Dietary studies of Trappist vegetarian and Benedictine nonvegetarian monks indicate that they differ significantly in the percentage of calories which they derive from fat (Trappist: 25 per cent, Benedictine: 45 per cent). Biochemical studies comparing the vegetarians with the nonvegetarians reveal that most serum lipids are significantly lower in the former group.

Adipose biopsy specimens were obtained in 33 members of both groups who were in the same age group and had consumed their respective diets for 3 to 10 years. The fatty acid composition of the adipose tissue was analyzed with gas chromatography. This was compared with dietary fatty acid intake obtained via repetitive diet records on each individual. Comparing the fatty acid composition of the adipose tissue with the fatty acid composition of the dietary intake, there appears to be a moderate correlation between these 2, with the linoleic acid showing the best correlation.

Electrocardiographic and Hemodynamic Findings in Pulmonary Stenosis with Intact Ventricular Septum

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Electrocardiographic data on 53 patients (aged 5 to 58 years) with pulmonary stenosis were correlated with the hydraulic load on the right ventricle. Right-heart-catheterization data allowed classification into mild (31 cases), moderate (12), and severe stenosis (10). Dye-dilution curves and saturation data revealed no left-to-right shunts.

In the mild group, the systolic pressure gradient (PG) was < 50 mm. Hg, pulmonary-valve resistance (PVR) < 600 dynes/sec./cm.$^{-5}$, pulmonary-valve area (PVA) > 0.66 cm.^{2}, and right ventricular work index (RVWI) < 2.2 Kg./min./M^2. The severe group had a PG > 100, PVR $> 1{,}200$, PVA < 0.50, and RVWI > 3.7.

Thirty-one patients had mild stenosis: height of the R wave in V_1 (R_{V_1}) was < 8 mm. in 27, sum of R_{V_1} and the S wave in V_6 (S_{V_6}) < 15 mm. in 26, frontal QRS-T angle $< 50°$ in 25, and horizontal QRS-T angle $< 50°$ in 24. Ten patients had severe stenosis: R_{V_1} was > 16 mm. in 8, R_{V_1} plus $S_{V_6} > 23$ mm. in 7, frontal QRS-T angle $> 110°$, and horizontal QRS-T angle $> 100°$ in all.

Correlation of the electrocardiogram with dynamics was better in the severe than in the moderate group. Calculations utilizing flow (PVR and PVA) and body surface area (RVWI) correlated better with the electrocardiogram than did pressures alone.

Thirty-seven patients had "incomplete right bundle-branch block" patterns; of these, 22 could be considered as having "diastolic overload" patterns. Of the 8 with "RV systolic overload patterns," 7 had severe stenosis.

Familial Cardiomyopathy

Edward J. Battersby, Baltimore, Md., and George G. Glenner, Bethesda, Md.

The familial aggregation of isolated myocardial disease is rare in the absence of somatic myopathy or Friedreich's ataxia. A sibship of 11 members has been studied of which 5 are presumed to have been affected with an unexplained cardiomyopathy. Two have been autopsied and a fine interstitial myocardial scarring has been found. The major coronary arteries were patent and there was no evidence of rheumatic changes or abnormal glycogen deposition.

The clinical course of the 2 siblings, 1 still surviving, followed closely by the authors was quite similar. Both had disabling runs of rapid paroxysmal atrial tachycardia. There were gross conduction defects on the electrocardiograms. The pulse pressures were narrow; the heart quiet; the second sound in the pulmonic area fixedly split. Exercise intolerance was out of proportion to clinical signs of failure.

Another sibling had a recurrent pericardial effusion that required numerous pericardial paracenteses. She died following pericardial surgery. Except for the thickened pericardium, the gross and microscopic appearance of the heart was identical with that of a sibling.

No etiology can be assigned to this disease nor are any specific measures of avail. Therapy for congestive failure is indicated but seems to accomplish little. Unexplained early deaths in first cousins, the presence in both sexes, and a previous absence of the disease in the family suggest an autosomal recessive genetic inheritance as a possible cause.

Alterations in Fibrinolytic Parameters during Recovery from Diabetic Acidosis

Samuel Bellet, George Tsitouris, Jean Schraeder, and Herschel Sandberg, Philadelphia, Pa.

The recent successful employment of fibrinolytic enzymes in the therapy of thrombo-embolic states has stimulated a growing interest in the thrombolytic mechanisms of the human organism. Increased fibrinolytic activity has been reported appearing in the blood under conditions of stress, following pulmonary and open heart surgery, and in certain obstetrical complications. A decreased tendency for fibrinolysis due to increased inhibitors to the plasmin-plasminogen system has been reported in thrombo-embolic diseases. It was, therefore, decided to investigate fibrinolytic parameters in patients recovering from diabetic acidosis.

Oxalated blood samples from 11 patients with diabetes mellitus were drawn during the state of severe acidosis and again when this condition had been somewhat ameliorated by means of insulin

and parenteral fluid therapy. The following studies were performed on these samples: (1) lysis time of a standard fibrin clot by undiluted and diluted plasma; (2) euglobulin lysis time; (3) plasma fibrinogen concentration; (4) antithrombolytic lysis times against serial dilutions of a commercial preparation of human fibrinolysin. Similar studies were run using normal controls.

The antithrombolytic lysis time and undiluted plasma lysis times during the state of diabetic acidosis were considerably shorter than those of the control group. During recovery from the acidotic state, however, this fibrinolytic activity was very markedly increased. The fibrinogen concentrations, diluted plasma and euglobulin lysis times were diminished to a lesser degree. These changes were believed to be due to a powerful activator of plasminogen released into the blood stream by the administration of insulin.

Effect of Nicotine on the Coronary Blood Flow in the Presence of Coronary Insufficiency: Experimental Study in Dogs

Samuel Bellet, James W. West, Paolo Rossi, Ugo Manzoli, and Otto F. Muller, Philadelphia, Pa.

The object of these experiments is to determine the effect of nicotine in the presence of coronary insufficiency. This state was produced (1) by ligation of the anterior descending branch of the left coronary artery; (2) by the application of rings containing casein around the circumflex and the anterior descending branch of the left coronary arteries. Because the casein swells, a gradual narrowing of the lumen of the coronary arteries results which may be reduced by 50, 75 per cent or may be almost entirely occluded. The effects of the infusion of nicotine and inhalation of tobacco smoke on the coronary blood flow and the electrocardiogram were noted and compared with those in a control group. The following results were obtained. The infusion of nicotine and inhalation of tobacco smoke resulted in a marked decrease in tolerance to nicotine. The coronary blood flow, which increased appreciably in normal dogs following the infusion of nicotine, was accompanied by a relatively slight change and, in some instances, was associated with a decrease in coronary blood flow. In group 2, with varied degrees of coronary artery narrowing, it was found that the coronary blood flow was increased less as compared to that of normal controls. The effect on the coronary flow appeared to be related to the degree of coronary artery narrowing. These findings suggest that coronary insufficiency produced in various ways results in the inability of the coronary blood flow to increase to the degree observed in a normal control group.

Massive Steroid Therapy in Acute Rheumatic Activity and Carditis

Gordon Bendersky, Daniel Mason, Ella Roberts, Jeannette C. Mason, Margaret A. Milliken, and Marion B. Wikingsson, Philadelphia, Pa.

A group of children with rheumatic activity, many of whom had concomitant rheumatic carditis, were given long-term massive doses of dexamethasone. This consisted of daily doses of 6 to 10 mg. of this drug (depending upon weight and age) for 6 weeks, with gradually decreasing dosage over the next 4-week period.

In every case, there was beneficial effect as shown by return of temperature to normal, decrease in cardiac rate, disappearance of joint signs, decrease in cardiomegaly, abolition of first degree heart block on the electrocardiogram, return of the sedimentation rate and C-reactive protein to normal and decline in ASTO titer (when initially elevated). In 4 patients with moderate to severe chorea, all neurologic signs disappeared within 48 to 72 hours. When congestive failure was due to acute carditis, this disappeared with dexamethasone therapy without the use of digitalis in some cases.

There was a tendency for the white blood cell count to become elevated with dexamethasone therapy. Complications from the use of this drug included hypertension, diabetes mellitus, moon facies, acne, abdominal and breast striae, epileptiform seizures (with normal encephalographic findings), adrenal depletion, osteoporosis, acute psychoses, and increased incidence of staphylococcic infection.

Serum electrolyte patterns (sodium, potassium, chloride) did not vary significantly during the course of therapy.

After 6 to 10 weeks of therapy, there was a 20 per cent rheumatic activity relapse rate. It was too early to attempt to evaluate the degree of residual valvular damage in this group of patients compared with a previous control group.

Side Effects of Nicotinic Acid in Treatment of Hypercholesterolemia

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During a 5-year period, we have used nicotinic acid (1.5 to 6 Gm. daily) in treating 67 patients with hypercholesterolemia. Plasma cholesterol levels less than 250 mg. per 100 ml. were achieved in 41 of the 51 persons completing at least 1 year of therapy and whose mean pretreatment level was 327 mg.

Cutaneous flushing, noted initially by all patients, usually subsided and was not a serious problem. Gastrointestinal symptoms occurred in

11 patients and caused 4 to discontinue treatment. Hyperglycemia developed in 21 of 31 persons tested; 19 exhibited glucose-tolerance curves simulating diabetes mellitus, but 14 of the 16 who were rechecked reverted to normal after withdrawal of nicotinic acid. Mild hyperuricemia occurred during treatment in 16 of 26 patients tested, and single episodes of gout developed in 2.

During treatment, at least 1 abnormality of tests relating to hepatic function occurred in 23 of 52 patients; jaundice, which subsided promptly when use of the drug was stopped, developed in 2. Biopsy done in 1 of these patients demonstrated centrilobular biliary stasis and cellular necrosis. Hepatic biopsy in 2 others during treatment gave normal results, but histologic studies at necropsy disclosed mild fatty change in 7 of 9 patients dying of vascular disease during or following administration of nicotinic acid.

Although these side effects of large doses of nicotinic acid do not contraindicate its use in most instances, they indicate the need for careful observation of patients so treated on an investigational basis.

Relation of Fat Tolerance to Coronary Atherosclerosis

Donald Berkowitz, David M. Sklaroff, John J. Spitzer, and William Likoff, Philadelphia, Pa.

Considerable attention is being focused on hypercholesterolemia as an important factor in the genesis of atherosclerosis, and many regimens, both dietary and drug, are being advocated in an attempt to normalize cholesterol levels.

On the basis of more precise methods for studying lipid metabolism, notably radioactive fat-tolerance tests, evidence is at hand which indicates that abnormal fat tolerance is more frequently present, and that this may represent a more fundamental disturbance than that reflected by an elevated blood lipid fraction. Furthermore, treatment of patients with coronary artery disease and hypercholesterolemia with various of the cholesterol-lowering agents such as nicotinic acid, sitosterol, and triparanol, has resulted in a reduction in the cholesterol level in a certain per cent of those treated, with no concomitant improvement in the fat tolerance. We do not believe it likely, therefore, that these drugs produce any favorable changes on the atherosclerotic process.

Attempts to improve fat tolerance by weight reduction, heparin, and certain other related preparations, with or without a simultaneous lowering of the cholesterol, would appear a more rational approach to the problem.

Effect of Lipemia on the Disappearance Rate of Intravenously Administered Radioactive Fat

Donald Berkowitz, John J. Spitzer, Millard N. Croll, and David M. Sklaroff, Philadelphia, Pa.

The use of intravenous radioactive fat is currently being explored as a new tool to study lipid metabolism. Tolerance tests using 2 to 3 cc. doses of I^{131}-iodinated triolein have demonstrated that over 75 per cent of the injected fat has already left the circulation after 15 minutes. Although the rate of disappearance is somewhat slower in patients with certain lipid disorders such as essential hyperlipemia and hypothyroid disease, this difference may at times not be very marked.

In an attempt to increase the sensitivity of the procedure, a priming test meal of 250 cc. of light cream was administered orally and the effect of the resulting lipemia noted on the disappearance rate of radioactive fat injected intravenously 2 hours later.

A uniform elevation of the blood radioactivity levels occurred in these instances when compared to corresponding time intervals when the fat was administered in the fasting state. In addition, the disappearance rate of the tagged triolein was much slower, thus giving a much more precise distinction between normal and abnormal states. Simultaneous determinations of the blood lipid fractions showed that the amount of radioactivity at any specific time, and its rate of disappearance from the blood was, in essence, a function of the level of the serum triglyceride concentration.

Further modifications of this prefeeding principle are in progress in an effort to evolve a simple and rapid intravenous fat-tolerance test.

Blood Pressure Measurements in Obese Persons

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This investigation concerned itself with the falsely high blood pressure readings which are said to be common in obese people. It consisted of simultaneous direct intra-arterial blood pressure measurements by means of an electromanometer, and indirect measurements with the auscultatory method. One hundred subjects were used and were grouped according to their Ponderal Index W/H, weight per inch of height. Sixty-one subjects were obese, 39 were nonobese.

The indirect method generally underestimates systolic and overestimates diastolic pressure. This holds for lean persons as well as for moderately obese persons.

The discrepancies between the direct and indirect methods were usually minor among the lean and the moderately obese subjects and went in both directions. Falsely high blood pressure readings in lean and moderately obese persons are not common.

In extremely obese persons the indirect method is subject to considerable error. In 8 out of 10 persons, the systolic pressure was overestimated by

from 6 to 51 mm., and in 9 out of 10 such persons the diastolic pressure was overestimated by 4 to 35 mm. The extent to which systolic pressure is overestimated in extremely obese persons can be much greater than was heretofore known. Overestimations of 44, 50, and 51 mm. occurred in 3 of our stoutest subjects. Falsely high readings, common in extremely obese subjects, are caused by the large size of their arms. They are usually avoidable or at least foreseeable.

Demonstration of Penicillin Inhibition by Pharyngeal Flora in Patients Treated for Streptococcal Pharyngitis

Stanley H. Bernstein, Maxwell Stillerman, and Charles M. Samet, New Hyde Park, N. Y.

Bacteriologic relapse follows adequate penicillin treatment of streptococcal pharyngitis in 10 to 12 per cent of patients. This may be due to other concurrent pharyngeal organisms which inhibit the action of penicillin. A new method has been developed to test this hypothesis. Cultures from the pharynx were obtained from 65 patients with pharyngitis due to group A beta hemolytic streptococci before, during, and after 10 days of oral administration of phenoxymethyl penicillin (750 mg. per day). A group of 85 patients with untreated nonstreptococcal pharyngitis was similarly studied. Swabs were incubated in eugon broth for 48 hours. The following method was used to demonstrate organisms capable of inhibiting penicillin action. A standard beta hemolytic streptococcus, sensitive to .03 units per ml. of penicillin, was streaked on blood agar. Plastic cups, equidistantly spaced, were embedded in the agar. To each cup was added .1 ml. (0.2 units) of purified phenoxymethyl penicillin and .1 ml. of the test cultures. After incubation, inhibition of streptococcal growth was measured by the lack of the zone of hemolysis surrounding each cup. In both groups, 16 to 18 per cent of cultures taken at the onset of illness carried penicillin-inhibiting organisms. These organisms were not found during and after therapy in 35 patients with streptococcal pharyngitis cured with penicillin. However, in 8 of 10 patients relapsing after therapy, penicillin-inhibiting organisms were found. These findings suggest that penicillin inhibition by concurrent bacterial flora may govern the therapeutic response of streptococcal infections. Identification of inhibiting organisms and suggested modifications of therapy to overcome this effect have also been studied.

Comparative Effects of Thyroxin Analogs as Hypocholesterolemic Agents

Maurice M. Best and Charles H. Duncan, Louisville, Ky.

Several analogs of thyroxin exert a disproportionate effect on cholesterol metabolism of the rat as compared to the naturally occurring L-thyroxin. Four such compounds, tetraiodothyroformic acid (200 to 400 mg. daily), dimethyldiiodothyroformic acid (200 mg. daily), D-thyroxin (10 mg. daily), and D-triiodothyronine (1 to 2 mg. daily), were selected on the basis of the animal studies and compared to L-thyroxin (0.2 mg. daily) in the hypercholesterolemic human. Fourteen euthyroid patients have been observed continuously for approximately 3 years during which placebos and 2 or more thyroxin-like compounds were administered alternately and their effects on serum cholesterol noted.

Significant reductions of serum total cholesterol resulted from the daily administration of each of the 4 analogs. The reduction was sustained for periods of 16 to 38 weeks of treatment with no tendency to escape. With the substitution of placebos, serum cholesterol returned to the pretreatment range. No tachycardia, weight loss, or other evidence of hypermetabolism was observed to result from the drugs, although in 1 patient there was possibly an increase in effort angina. No serious toxic effects were observed, although 3 patients exhibited iodide reactions while receiving 1 of the 2 formic acid analogs. The mean reduction of serum cholesterol resulting from the analogs (20 per cent of pretreatment control level) was somewhat greater than that resulting from L-thyroxin. During the periods of analog administration, mean serum cholesterol was 62 mg./100 ml. below the mean control level of 312 mg./100 ml.

Effect of Hypothermia in Experimentally Produced Arrhythmias

Ezra J. Beyda, Philadelphia, Pa., Sol Alvarez, Chicago, Ill., Otto F. Muller, and Samuel Bellet, Philadelphia, Pa.

Rapid ectopic rhythms (atrial fibrillation, atrial tachycardia and atrial flutter) were produced in 16 open-chested and 9 intact animals by the application of aconitine to the right atrium. Following the production of the arrhythmia, the ventricular rate during normothermia ranged from 160 to 320 beats per minute. Hypothermia (temp. 78 to 92 F.) was then produced in these animals. In practically all of the experiments, marked slowing of the ventricular rate occurred (this ranged from 80 to 120 beats per minute). On rewarming, the heart rate rose from an average of 93 per minute during hypothermia to 175 per minute when the temperature was raised. Sinus rhythm acquired during hypothermia persisted in most instances. The blood pressure, which dropped significantly during the rapid ectopic rhythm, was slightly increased during the period of slowing obtained with hypothermia. The results obtained in the experi-

mental animal would appear to have a bearing on certain refractory arrhythmias in the human subject.

Analysis of Deaths from Intracardiac Surgery

Emil Blair, R. Adams Cowley, Robert T. Singleton, Paul Hackett, and William G. Esmond, Baltimore, Md.

This study is a detailed analysis of deaths in 100 cases of open heart surgery in which there were 30 deaths (27 per cent). Four died during preoperative preparation. Nine died on the operating table. Cardiovascular collapse was the most common cause of death. Respiratory failure, metabolic acidosis and hemorrhage were noted in decreasing frequency. Cardiovascular collapse occurred most often in the seriously ill infant with complex anomalies and in the adult with chronic severe valvular disease.

In those patients with acquired heart disease, the mortality rate was 29 per cent (4/14) below the age of 40 and 44 per cent (4/9) over 40. In the congenital group, a 50 per cent (12/24) mortality rate was observed in infants while only 11 per cent (4/38) was observed in the age group 4 to 15 years.

When hypothermia with circulatory occlusion was utilized, the death rate was 14 per cent (5/36) over-all and only 7 per cent (2/33) for the secundum defects and valvular pulmonic stenosis. Unabridged statistics reveal 33 per cent (25/75) mortality in the pump oxygenator cases. The pump time became a significant factor only when it exceeded 2 hours.

For the most part, death from cardiac surgery is not due to abstruse causes but rather to the same reasons generally observed for all forms of thoracic surgery in poor-risk cases. In the older age group, coronary artery disease is a contributing factor. Severe pulmonary hypertension was a significant contributing factor in the infant death rate. By eliminating all preventable deaths, the mortality rate would stand at about 10 per cent (11/110). Improvement in diagnosis, operative technics and postoperative care should result in a significant reduction in mortality rates.

Role of Hypothermia in Intracardiac Surgery

Emil Blair, R. Adams Cowley, Robert T. Singleton, Paul Hackett, and William G. Esmond, Baltimore, Md.

By lowering metabolic requirements for oxygen, blood perfusion can be reduced or even totally suspended for prolonged periods. This was the original, and remains the current, basis for direct heart surgery under hypothermia alone or in conjunction with total bypass. Circulatory occlusion fell into disrepute because of the high incidence of ventricular fibrillation and the limitation of time for surgery. These 2 problems were mitigated by: (1) limiting this procedure to only the simplest defects (secundum interatrial septal defects and pulmonary valvular stenosis); (2) moderating the level of hypothermia (thereby reducing the hazard of fibrillation); and (3) not using drugs either for attempted defibrillation or for cardioplegia. Hypothermia alone in the range of 29 to 26 C. permits safe occlusion from 10 to 15 minutes.

The advantages gained from the use of hypothermia with bypass are: (1) reduction in blood flow; (2) elimination of metabolic acidosis; and (3) extension of safe perfusion time. At normal body temperature, safe perfusion has been limited to 40 minutes or less. With hypothermia of 32 to 30 C. pump time up to 2 hours is permissible with safety. With this technic, repair of most complex defects is possible. Total bypass with cold arrest is the newest and most promising application of hypothermia to intracardiac surgery.

Our experiences are based upon over 100 cases, using the technics listed above. Hypothermia alone remains a simple, safe and effective tool when used judiciously. When combined with bypass, potentialities of artificial perfusion can be greatly extended.

Coronary Arterial Calcification

David H. Blankenhorn, Los Angeles, Calif.

Coronary arterial calcifications are the most common radiopaque lesion of the heart. Although improved radiologic technics now lead to discovery of an increased number of coronary arterial calcifications in living man, the prevalence of these lesions is frequently underestimated at autopsy. Autopsy study of the radiographic pattern of coronary arterial calcification in 89 adults indicates that a unique situation exists in this artery. Calcification invariably occurs in atheromatous lesions and Mönckeberg's medial calcification does not exist. Massive coronary calcification is most frequently seen in hearts exhibiting grossly dilated coronary arteries and it seems possible that dilation effects tolerance to severe atherosclerosis, permitting survival for a sufficient period to allow extensive calcification. Small calcifications of the coronary artery have been found in young men (aged 30 to 50) dying suddenly of ischemic heart disease. These men apparently could not tolerate coronary atherosclerosis for a sufficient period to develop extensive calcification. These findings are relevant to the design of experiments investigating the prevalence of atherosclerosis by search for manifest ischemic heart disease, because they demonstrate certain individuals in whom the extent of atherosclerosis is inversely proportional to the

clinical significance of lesions. These findings also indicate that small calcifications discovered in a young man have much greater significance than extensive calcification at a later age.

New Methods of Serum Glyceride Analysis

David H. Blankenhorn, Los Angeles, Calif.

The glyceride fraction of serum lipids has been shown to play an important role in energy metabolism and to affect blood oxygen transport. It may also affect blood coagulation. This paper presents an improved system of blood glyceride analysis. To find patients with abnormal blood glycerides, a screening technic has been devised. This is a modification of the total cholesterol determination of Abell, Brodie, Levy, and Kendall which allows concurrent total cholesterol and total lipid determinations. When total cholesterol and total lipids are known, the lower limit of serum glyceride content can be estimated. To furnish further information, a simple microchromatographic method employing Florisil has been devised. This technic allows determination of total glycerides, triglycerides, diglycerides, and monoglycerides in 1 cc. of serum. The adsorbent properties of Florisil have been found to be constant from lot to lot and to effect sharp separation of lipid classes. Ninety-seven to 99 per cent recovery of added glycerides can be achieved. The existence of monoglycerides and diglycerides in human blood can be demonstrated with this system.

Effect of Nicotinic Acid, Stearic and Linolenic Acid, Heparin, and Estrogenic Hormones on Uptake and Dispersal of Cholesterol in Aortic Endothelial Cells Grown in Tissue Culture

Ancel U. Blaustein and Marilyn Rosenblat, New York, N. Y.

Rat aortic endothelial cells were grown in tissue culture according to the method described by Rutstein et al. When sufficient explantation occurred, transplants were placed in a double cover slip Maximow slide. Groups of cells were exposed to media containing serum derived from patients whose cholesterol levels ranged from 350 to 560 mg. per cent. On the third day under brite lite or phase microscopy, lipid deposits were seen in the cell cytoplasm. As exposure to cholesterol continued, a marked increase in uptake was demonstrated by Sudan Black B stains and specifically by the Lieberman-Burchard reaction.

The following experiments were performed.

1. Nicotinic acid (5 per cent) plus high cholesterol serum were added to the feeding media. Explant cells were exposed to the composite media in Maximow slides for 2 weeks. The media were changed every third day.

2. Linolenic acid plus high cholesterol were added to the feeding media as above for 1 week.

3. Cells were exposed to stearic acid and high cholesterol as with linolenic acid.

4. Heparin and high cholesterol serum were added to the feeding media and cells exposed to the composite mixture.

5. Conjugate estrogens were added to the media, in addition to high cholesterol serum. The cells were exposed to this mixture.

Findings: Five per cent nicotinic acid appreciably decreases the uptake of cholesterol by the cells. It also causes the dispersal of lipid from cells already laden with it. Linolenic limits the uptake of cholesterol while stearic acid enhances it. Estrogens and heparin do not influence uptake or dispersal of cholesterol.

Bacterial Endocarditis in Children with Heart Disease

Sidney Blumenthal, Sylvia P. Griffiths, and Beverly C. Morgan, New York, N. Y.

A review of experience with 58 children with bacterial endocarditis superimposed upon heart disease indicates this is not a rare complication and that patients of all ages, including infants, may be affected. Although we have not noted any decrease in the incidence of this disease since the introduction of antibiotics, its clinical manifestations have changed dramatically.

In the majority, infection was superimposed upon a congenital cardiac malformation; rheumatic heart disease was a less common underlying disorder. Unexplained fever and fatigue were usual admitting complaints. Additional symptomatology reflected the underlying cardiac pathology and predilection for vegetations to develop at specific sites. Involvement of the endocardium of the right side of the heart and pulmonary artery was common. Patients with tetrad of Fallot developed symptoms secondary to hypoxia attributable to vegetations resulting in obstruction to pulmonary blood flow.

Bacteriologic studies were as vital in confirming diagnosis and planning treatment as in the management of patients with meningitis. Bacterial endocarditis was uncommon if blood cultures were sterile, providing an adequate number (6) of sufficient quantity (10 ml.) had been obtained from a patient who was not receiving antibiotics. Antibiotic treatment was successful in all patients with endocarditis due to *Viridans streptococci* and in less than half of those with endocarditis due to *Staphylococcus aureus*. A therapeutic regimen should be based upon identification of the causative organism and determination of its in vitro sensitivity.

The prevention of bacterial endocarditis pre-

upposes knowledge of factors initiating bacteremia and the nature of the offending organism. Therapeutic blood levels with a bactericidal agent must be achieved for adequate prophylaxis.

Coronary Heart Disease as a Cause of Congestive Heart Failure

Herrman L. Blumgart, Paul M. Zoll, Boston, Mass., and William Gibson, Detroit, Mich.

In patients with congestive heart failure, the etiologic diagnosis of arteriosclerotic heart disease is commonly made after the exclusion of valvular and hypertensive heart disease and other obvious causes. Sharp exception to this practice has been expressed by some observers who ascribe congestive heart failure in the absence of obvious cause to senile changes in the myocardium rather than to coronary atherosclerosis. To ascertain the validity of this term, a series of 1,300 consecutive autopsies was reviewed in which the coronary arteries had been examined by the injection and dissection technic.

Congestive heart failure had been present in 200 of the cases for at least 8 weeks. After valvular and hypertensive disease and other rarer causes were excluded, 23 cases remained. In 20 of them angina pectoris or myocardial infarction had been present clinically to support coronary disease as the etiologic basis for the congestive failure. All 23 hearts showed extensive coronary arterial obstruction and almost all showed myocardial fibrosis or infarction. Brown atrophy or changes of the "senile heart" other than coronary disease were not found. Cardiac hypertrophy was present in 18 of these 23 hearts. These findings demonstrate that coronary atherosclerosis alone may produce congestive heart failure by impairment of myocardial function that is usually evidenced at post mortem by myocardial fibrosis or infarction. When congestive heart failure is present clinically, the etiologic diagnosis of coronary heart disease may be made with a high degree of confidence if other forms of heart disease are not evident.

Percutaneous Left Atrial Puncture: Clinical Correlation and Inherent Errors

Richard W. Booth, John M. Hartman, Charles F. Meckstroth, and Joseph M. Ryan, Columbus, Ohio

Many reports regarding left heart catheterization emphasize the hazards of percutaneous atrial puncture. This communication describes the clinical application of this technic, emphasizes its simplicity and details its shortcomings.

Of 137 patients studied, only 6 had significant complications. No mortality occurred. The Fisher technic was employed. Absolute pressure measurements and valve gradient determinations were made by standard methods. Indicator-dilution curves were done and, if feasible, cardiac output and valve measurements were calculated.

Pure mitral stenosis was encountered in 31 cases, mitral regurgitation combined with some stenosis in 70, aortic stenosis in 20. The remainder had combined aortic and mitral lesions.

Comparing clinical evaluation to catheterization data, good correlation existed regarding the severity of pure mitral stenosis and aortic stenosis in approximately 50 per cent. In the remainder, however, mitral stenosis was often clinically overestimated while asymptomatic aortic stenosis was underestimated. This shows the hazard of relying solely on clinical judgment.

Although the electrocardiogram generally correlated well with the hemodynamic severity of mitral and aortic stenosis, 18 per cent with significant mitral stenosis (valve area less than 1.5 cm.^{2}) had normal electrocardiograms.

Radiographically, neither left atrial volume nor Kerley's lines correlated with atrial pressure or valve resistance.

Significant mitral or aortic regurgitation produces lower cardiac outputs than actual valve flows resulting in factitious reduction of valve areas. Large CV waves may not represent mitral regurgitation when left atrial pressure is high. Undetected minimally damped pressure curves will reduce gradients, producing erroneously large valve areas.

Electrocardiogram in Marfan's Syndrome

Dorrance Bowers, Kelowna, B. C., Canada

Sixty-three electrocardiograms from 55 Canadian patients with Marfan's syndrome have been collected and reviewed. In some patients, the cardiovascular "complications" of Marfan's syndrome were associated with electrocardiographic abnormalities; in some patients with serious cardiovascular abnormalities (for example, aneurysm of the aorta or pulmonary artery), the electrocardiograms were normal.

Thirty-nine per cent (12 of 31) of male patients and 17 per cent (4 of 24) of female patients had abnormal electrocardiograms; 23 per cent (7 of 30) of patients under 20 years of age and 36 per cent (9 of 25) of patients older than 20 years had abnormal electrocardiograms.

The most common abnormal electrocardiographic pattern (9 tracings from 8 patients, all male) was the pattern of left ventricular hypertrophy. This pattern was thought to reflect left ventricular hypertrophy resulting from aortic valvular insufficiency.

The second most common abnormal electrocardiographic pattern (found in tracings from 4 male and 3 female patients) consisted of S-T segment depression or T-wave inversion in leads II, III, and AVF. This pattern was thought to reflect right ventricular or biventricular hypertrophy, or to be an effect of digitalis.

Atrial fibrillation was recorded in 2 electrocardiograms, incomplete right bundle-branch block in 7, and complete right bundle-branch block in 1. There were no other significant disturbances of rhythm or conduction.

It was concluded that, in this group of patients, Marfan's syndrome is an abiotrophic disorder of the cardiovascular system frequently associated with nonspecific electrocardiographic abnormalities.

Hemodynamic Observations on the Function of the Left Atrium in Man

Eugene Braunwald, Charles J. Frahm, and John Ross, Jr., Bethesda, Md.

It has recently been emphasized by Sarnoff, Mitchell, and Gilmore that atrial contraction contributes to ventricular filling, but the clinical importance of this phenomenon has not been appreciated. The difference between left ventricular end-diastolic or left atrial "z" point pressure (LVEDP) and mean left atrial pressure (MLAP) provides a quantitative measure of left atrial function. This pressure difference expresses the ability of the atrium to contribute to left ventricular filling, to augment LVEDP, and thus to provide the stimulus for ventricular contraction while maintaining MLAP, and therefore pulmonary venous pressure, at a lower level. In 9 subjects without heart disease, and in 7 patients with hemodynamically trivial abnormalities, LVEDP–MLAP ranged from −4 to +3 and averaged 0 mm. Hg. When MLAP was elevated to an average of 19 mm. Hg in 6 subjects by means of rapid blood transfusion, LVEDP–MLAP remained low, averaging 0 mm. Hg. In 23 patients with left ventricular hypertrophy due to aortic valve disease, idiopathic myocardial hypertrophy, or coronary artery disease, the LVEDP averaged 21 mm. Hg; the LVEDP–MLAP averaged 6 mm. Hg and was less than 3 mm. Hg, the highest normal value, in only 2 patients. An atrial sound was easily audible in the majority of these patients.

These data emphasize the clinical importance of left atrial contraction in patients with left ventricular hypertrophy in whom left atrial contraction elevated LVEDP while maintaining MLAP and pulmonary venous pressure at a significantly lower level. These observations provide an explanation for the deleterious effects of atrial arrhythmias in patients with left ventricular hypertrophy.

Enzyme Inhibitors in the Treatment of Hypertension

Albert N. Brest and John H. Moyer, Philadelphia, Pa.

The use of enzyme inhibitors in the treatment of hypertension is currently being investigated. Several monamine oxidase (MAO) inhibitors, including iproniazid and 1-phenyl-2-hydrazinepropane have demonstrated significant antihypertensive abilities; and the hypotensive action of these compounds is further enhanced by the therapeutic addition of the thiazide derivatives. The MAO inhibitor nialamide has been used alone and in combination with thiazide derivatives in 40 patients with significant antihypertensive results; serious toxic or side reactions have not been encountered. The mechanism of hypotensive action of the MAO inhibitors remains undetermined. More recently, decarboxylase inhibitors have been investigated in hypertensive subjects. Fifteen patients were treated with α-methyl-3,4-dihydroxyphenylalanine and the antihypertensive effect of the latter drug was confirmed. The hypotensive action of the decarboxylase inhibitors appears to be due to the inhibition of the decarboxylation of dihydroxyphenylalanine to dihydroxyphenethylamine (dopamine). The subsequent synthesis of the sympathetic mediator, norepinephrine, is thereby reduced. In addition to their potential clinical usefulness, the enzyme inhibitors may ultimately provide additional insight into the pathogenesis of the hypertensive process.

Hemodynamic Technic for the Detection of Hypertrophic Subaortic Stenosis

Edwin C. Brockenbrough and Eugene Braunwald, Bethesda, Md.

In the presence of valvular aortic stenosis or of discrete subvalvular stenosis, the narrowed orifice is constant and its size is not altered by changes in the force of ventricular contraction. In hypertrophic subaortic stenosis the orifice narrows during systolic contraction of the hypertrophied muscle in the left ventricular outflow tract and the orifice size, therefore, is a function of the force of left ventricular contraction. In 75 patients proved to have the discrete, "fixed" type of aortic or subaortic stenosis, the beats following the compensatory pause after a premature ventricular contraction were always characterized by higher left ventricular systolic pressures and larger systemic arterial pulse pressures than the normal beats, i.e., arterial pulse pressure varied directly with left ventricular systolic pressure and with the duration of diastole. In all 9 patients proved to have hypertrophic subaortic stenosis, the beats following premature contractions always exhibited *lower* arterial pulse pressures than did the normal

bolts, i.e., arterial pulse pressure varied *inversely* with left ventricular systolic pressure and with the duration of diastole. The distinction between these 2 types of obstruction to left ventricular outflow may be established with confidence by this analysis of the effects of premature ventricular contractions on either the simultaneously recorded left ventricular and arterial pressure pulses, or on the arterial pressure pulses alone. The recognition of hypertrophic subaortic stenosis is essential in formulating a rational plan of treatment for all patients with obstruction to left ventricular outflow, and the hemodynamic technic described affords a simple but reliable diagnostic approach.

Surgical Considerations in Cerebral Vascular Insufficiency

Milton F. Bryant, Atlanta, Ga.

Considerable experience has now been accumulated which shows that approximately 30 to 35 per cent of patients with cerebrovascular insufficiency have stenotic or occlusive lesions in the extracranial portion of 1 or more of the 4 major arteries that supply the brain. Atherosclerosis is the usual cause of these obstructive lesions, although on occasion one may encounter embolic obstruction or obstruction due to arteritis. The atherosclerotic lesions have a distinctive topography. The proximal form occurs in the major vessels as they originate from the aortic arch. In the distal form the plaques are located in the vertebral and internal carotid arteries at their origin.

Proximal obstructions produce arterial insufficiency in the vessels to the upper extremities and to the brain depending upon the number of arteries involved at the aortic arch. The important physical findings are related to examination of the blood vessels in the upper extremities and neck. The extent and exact location of these lesions is established by aortography. Six patients have been operated upon with complete relief of symptoms.

Distal obstructions in the internal carotid artery usually produce symptoms and signs associated with insufficiency to the territory supplied by the middle cerebral artery. Bilateral carotid arteriograms are essential in establishing the diagnosis. Thirty patients have been operated upon with marked improvement in 65 per cent.

Obstructions in the proximal portion of the vertebral arteries produce symptoms similar to those associated with thrombosis of the posterior inferior cerebellar artery, or, if bilateral, symptoms of basilar artery insufficiency may occur. Transsubclavian vertebral arteriograms are necessary to confirm the diagnosis. Restorative operations have been performed in 12 patients. Improvement occurred in only 3 patients.

An aggressive approach, including arteriography in many instances, to the problem of recurrent focal cerebral ischemic attacks and to strokes in general is essential in order to outline the best treatment program for each patient.

Electrocardiographic Patterns of Injury, Ischemia, and Necrosis

Cesar A. Caceres, Washington, D. C.

Ischemic electrocardiographic patterns and initial QRS abnormalities similar to those of infarction have been reported, in the literature, in otherwise normal subjects. In this study, conventional surface plus intracavitary leads from 1 or more chambers were recorded during right and/or left heart catheterization in 50 subjects not suspected of having coronary artery disease. At least 2,500 electrocardiographic sequences were scrutinized per subject. The majority of subjects were observed to have repeated instances during which there were surface ventricular electrocardiographic patterns indistinguishable from those of acute injury, myocardial ischemia, or necrosis. These surface patterns were correlated to simultaneously recorded intracavitary leads as well as to chamber pressures. There was a constant association of abnormal surface electrocardiographic patterns like those seen in coronary artery disease, and intracavitary evidence of premature depolarization. Local cavity injury currents, when sustained, were also associated with evidence of premature depolarization of an area of myocardium. Electrical asynchronism between chambers was observed, at times associated with mechanical asynchrony. The observations suggest that similar mechanisms of production may be attributable to abnormal electrocardiographic patterns in normal subjects as well as to patterns obtained in disease states. The degree of premature depolarization of an area of myocardium or of an entire ventricle and the time lapse between atrial and ventricular depolarization suffice to explain most abnormal electrocardiographic patterns generally related to coronary artery disease.

Value of Intracavitary Electrocardiography

Cesar A. Caceres and Juan Calatayud, Washington, D. C.

Intracavitary electrocardiography is an indispensable tool in the proper control of cardiac catheterization. It is also of value in the study of electrical and mechanical activity of the heart. Intracavitary tracings from 1 or more chambers in 50 left and/or right heart catheterizations performed with simultaneous recordings of surface leads and chamber pressures were studied. The tracings demonstrated that localization of the catheter tip within a chamber was more precise with the intra-

cavitary electrocardiogram alone than with a combination of pressure curve and fluoroscopic image. Electrically precise localization of a chamber or a specific area within a chamber is possible. Use of the intracavitary electrocardiogram therefore reduces radiation-exposure time during cardiac catheterization to a minimum. Intracavitary leads allow early detection of injury currents within the heart. These local injury currents are observed in the majority of cardiac catheterizations. They herald the onset of severe arrhythmias, and if allowed to persist may be observed in surface leads. Intracavitary leads prevent a lack of awareness of the imminence of these events. Study of the morphology of intracavitary wave patterns provides information regarding the electrical activity of myocardial musculature not otherwise available under relatively normal conditions in the human subject. It is thus possible to observe changes in the sequences of myocardial activity during the time that surface leads change from normal to abnormal patterns, during complex arrhythmias, and during therapy.

Diagnostic Value of the Pulse Wave Contour in Obliterative Arterial Disease

Francis S. Caliva and Bruce Chamberlain, Syracuse, N. Y.

Arteriograms of 50 patients with blocks of the femoral artery have been classified according to involvement of other more peripheral vessels ("run-off"). In each patient, correlation was then made between the arteriograms and the contour of the pulse waves previously recorded from several locations on the leg and from the toe.

The change in pulse wave contour allowed prediction of the site of the block. The presence or absence of toe pulsations was found to correlate well with the adequacy of the "run-off." Furthermore, prediction of the patency of the popliteal artery as well as more peripheral vessels could be made by recording pulse waves during the time of occlusion in the region of these vessels. Digital blood flows, determined plethysmographically, added little additional information.

These findings emphasize the importance of recording pulse waves in patients with obstructive arterial disease. Not only can information derived from the arteriogram be supplemented, but in many cases the need for such films may be obviated. In view of the difficulties associated with arteriography as well as the radiation exposure to both patient and physician, the described technics should find much practical application.

Complete Transposition of the Great Vessels: An Electrocardiographic and Anatomic Correlation

Homobono B. Calleja and Don M. Hosier, Columbus, Ohio

Complete transposition of the great vessels, in which the aorta arises anteriorly from the right ventricle and the pulmonary artery posteriorly from the left ventricle, was studied. Fifty-three patients satisfied this definition as proven by autopsy and/or angiocardiography and surgery.

The $\bar{A}$QRS were in sextants IV and V of Bayley's triaxial system in 88.88 per cent. The P wave was tall and peaked or notched in 28.30 per cent; the P-R interval was normal in all but 1 patient. A Q wave in V_1 was present in 13.21 per cent. Marked right axis deviation and a Q wave in V_1 were not seen in patients below the age of 3 months. Right ventricular hypertrophy was diagnosed in 62.26 per cent; left ventricular hypertrophy in 15.09 per cent; and combined ventricular hypertrophy in 9.43 per cent. The electrocardiogram was considered normal in 13.21 per cent; all these patients were under the age of 1 month.

In 40 patients the type and number of shunts were noted. Ventricular septal defect was the only shunt present in 22.50 per cent; patent ductus arteriosus alone in 10 per cent; atrial septal defect in 5 per cent; and no shunt in 1 patient. Two or more shunts occurred in 52.50 per cent. The thickness of the ventricular walls was measured in 25 patients. Isolated right ventricular hypertrophy occurred in 36 per cent; isolated left ventricular hypertrophy in 8 per cent; combined ventricular hypertrophy in 52 per cent; and no hypertrophy in 4 per cent.

Myxoma of the Right Atrium

Frank L. Campeti, Earle B. Mahoney, and Paul N. Yu, Rochester, N. Y.

This paper describes clinical, physiologic and angiocardiographic studies of 2 patients with right atrial myxoma and a review of 14 reported cases.

Both patients had extreme fatigue and intermittent peripheral edema. One had exertional dyspnea and fainting spells. The cervical veins were distended with prominent *a* wave. A loud diastolic murmur was heard at the tricuspid area and at the apex. The erythrocyte sedimentation rate was markedly elevated. Radiologically, the heart was enlarged, involving mainly right atrium (RA) and right ventricle (RV) with normal pulmonary vascular markings.

Electrocardiogram showed low voltage and prominent P waves. Cardiac catheterization demonstrated: (1) low cardiac output and stroke volume at rest and during exercise; (2) normal pulmonary artery and pulmonary wedge pressures; and (3) a diastolic pressure gradient between RA and RV. Arterial indicator-dilution curves following injection of the indicator into the RA were distinctly different from those following injection into the RV. Cineangiocardiograms revealed

dramatic cyclic movement of the tumor in the RA and inflow chamber of RV.

Surgical removal of the tumor was accomplished in both patients with pump oxygenator. The first patient subsequently died, but the second patient is well.

Since the tumor can now be successfully removed, a correct preoperative diagnosis is of paramount importance. This may be achieved by: (1) a high index of suspicion; (2) awareness of this discrepancy between the patients' marked symptoms and paucity of cardiac findings; and (3) data obtained from cardiac catheterization, indicator-dilution curves and, specifically, angiocardiography.

Cardiac Index in Ambulatory Patients Estimated by a Precordial Dilution Curve

Kenneth M. Campione, Irene Anday, Maria Serratto, and David P. Earle, Chicago, Ill.

Four hundred and twenty-nine indexes in 240 ambulatory patients were calculated from radiocardiograms (time concentration curves of radioactivity) obtained by external precordial detection of intravenously administered I^{131}-labeled serum albumin. The mean cardiac index of 3.51 in 48 normal subjects agrees well with reports of other investigators using various technics. Results were reasonably reproducible.

Patients with evidence of congestive heart failure either in the past or present had significant reductions in cardiac index. Cardiac index increased in association with clinical evidence of improvement in cardiac status after treatment.

In the absence of congestive failure, mean cardiac index was increased in patients with borderline hypertension, normal in those with systolic hypertension, and frequently reduced in those with sustained diastolic hypertension, especially when evidence of myocardial involvement was also present.

Most patients with coronary artery disease but no evidence of congestive heart failure had normal cardiac indexes. A few patients with myocardial infarction in the past had rather marked reductions in cardiac index.

Patients with purely stenotic valvular lesions had normal cardiac indexes, while valvular insufficiency led to erroneously low "cardiac index" values regardless of the presence or absence of congestive heart failure.

Classification of radiocardiograms according to qualitative features showed some correlation with cardiovascular status. Prominent downslope fluctuations were recognized most often in radiocardiograms of patients with valvular insufficiency or septal defects. Radiocardiograms maintained a constant form over considerable periods of time in the absence of marked change in cardiovascular status.

Management of the Lungs during Heart-Lung Bypass: Report of an Experimental Study

Robert S. Cartwright, Thomas P. K. Lim, Ulrich C. Luft, and E. Mary Mostyn, Albuquerque, N. Mex.

In 20 experiments on dogs, total body perfusions were carried out employing a Kay-Cross pump oxygenator at the rate of 80 to 100 ml./min./Kg. body weight with venous drainage from the venae cavae including the azygos flow. In the first preparation, the pulmonary circulation consisted of a combination of the coronary venous and bronchial collateral flow. The lungs were either artificially ventilated with air at the rate of 1.5 to 4 L./min., were statically inflated at 7 to 15 cm. H_2O, or were allowed to remain passively deflated. Under these circumstances, the biochemical parameters of the pulmonary venous blood were compared with those of the systemic arterial blood with the following results: (a) with moderate ventilation, the former showed a relatively small deviation in oxygen saturation from that of the latter; (b) when the other methods were used, the difference in oxygen saturation was accentuated to 40.2 per cent with static inflation and to 59.9 per cent with passive deflation. In a second preparation, cross clamping the aorta and pulmonary artery at the level of the semilunar valves permitted only the bronchial collateral flow to perfuse the lungs. In this case, static inflation caused the least deviation in the oxygen saturation, carbon dioxide tension, and hydrogen ion concentration of the pulmonary venous blood.

These data indicate that during cardiopulmonary bypass the physiologic integrity of the lungs is best preserved: (a) with moderate ventilation when the combined coronary venous and bronchial collateral blood circulates through the pulmonary vascular bed; and (b) with static inflation when the bronchial flow is the sole perfusate.

Determinations of the Limit of Reactivity of the Coronary Vascular Bed

Robert B. Case, Douglas M. Griggs, Jr., and Richard N. Pierson, Jr., New York, N. Y.

Coronary vascular resistance (CVR) was studied in the dog while perfusing the left main coronary artery by an occlusive Sigmamotor pump with blood supplied from the femoral artery. Pressure in the coronary circuit, aortic pressure, right atrial pressure, and coronary flow were simultaneously recorded. Coronary flow was reduced stepwise from overperfusion values to coronary insufficiency levels. Calculated CVR remained initially at a plateau as coronary flow was reduced. With

further reduction of flow, a rapid fall in CVR occurred, terminating in a second plateau at coronary insufficiency levels. The 2 plateaus of this curve are believed to represent the positions of maximal constriction and dilation of the coronary arterioles, while the region between represents the area of active arteriolar adjustment.

When studies were repeated during different levels of induced anemia, the curves were similar in shape, but the area of rapid CVR change occurred at correspondingly higher coronary flows. This indicates that the rapid CVR changes are related to oxygen availability and not to a hydraulic effect. The limits of reactivity were also seen to change with arterial oxygen content.

Lysis of In Vitro Thrombi by Purified Plasmin

Arthur B. Chandler, Augusta, Ga.

The effect of plasmin was tested on in vitro thrombi produced by causing blood to flow in a circular plastic tube rotated on a slanted turntable. Such thrombi, strikingly similar to in vivo thrombi, are composed of clumps and columns of agglutinated platelets bound together by anastomosing strands of fibrin.

In each of 52 experiments, replicate thrombi were made in 4 polyvinyl chloride plastic circular tubes, each containing 1 ml. of blood. Human fibrinolysin reconstituted in buffered saline was introduced into 2 tubes in amounts of 85 to 255 units/ml. of blood. The other 2 tubes were paired saline controls. Then, both pairs were rotated simultaneously at room temperature. One pair was stopped when thrombi formed in both tubes (10 to 20 minutes); the thrombi were fixed in formalin. The other pair was rotated an additional 40 minutes. Thrombolysis in the plasmin tube was correlated with dosage; 255 units dissolved a thrombus in 40 minutes. Films of the dissolved thrombi contained numerous platelet clumps. Two hundred and fifty-five additional units of plasmin separated the clumps into individual platelets after agitation for 1 to 2 hours.

In these experiments, plasmin lysed in vitro thrombi; higher dosage and longer exposure were required to separate agglutinated platelet clumps than to dissolve the fibrin bonds between them. Further experiments indicate that thrombolysis is less effective if plasmin is added after rather than before formation of in vitro thrombi.

Correction of Complete Heart Block by a Transistorized, Self-contained, and Implantable Pacemaker

William M. Chardack, Andrew A. Gage, and Wilson Greatbatch, Buffalo, N. Y.

Although chronic atrioventricular block has been successfully corrected by a variety of external electrical pacemakers, 2 difficulties have been encountered with pacemaking on a long-term basis. First, a rise in threshold currents has been observed with monopolar electrodes so that after a few weeks the stimuli required produce unpleasant side effects. A second major drawback of external devices has been the necessity of having a lead wire come out through the skin. This may lead to infection and places obvious restrictions on the patient's activities.

Recent evidence by S. W. Hunter et al. indicates that bipolar electrodes have low and stable thresholds. This has been confirmed in our laboratory and has led to the design of a miniaturized self-contained and implantable pacemaker.

The device measures only 5 cm. in diameter and 1.5 cm. in thickness, including its battery supply. The current drain is so low that a lifetime of from 5 to 6 years can be expected. Since the unit is implanted subcutaneously, it may then be easily replaced under local anesthesia without disturbing the electrode on the myocardium. Considerable experimental data on electrode and pacemaker design have been accumulated and analyzed.

Clinical experience has been obtained in 9 patients with extremely gratifying results. Several of these pacemakers have now been used continuously in patients for periods in excess of 3 months at the time of this writing.

Altered Relationship Between the Pulmonary Ventilatory Resistance and the Lung Volume in Various Cardiopulmonary Disorders

Tsung O. Cheng, Brooklyn, N. Y.

It has not received much emphasis until recently that the pulmonary resistance to ventilation varies with the state of inflation of the lungs. Pulmonary resistance was measured during both expiration and inspiration throughout the entire range of the vital capacity, using the multiple interrupter technic described by Clements and Elam and modified by Cheng, Godfrey and Shepard. The pattern of pulmonary resistance versus lung volume varies very little among the normal subjects. At and near maximal inspiration the resistance has a low value and it remains low throughout most of the vital capacity until near the maximal expiratory position where it changes rather abruptly to very high values. Inspiratory and expiratory resistance values are practically identical in normal subjects, although the former is frequently lower than the latter at a given lung volume. However, in patients with various cardiopulmonary disorders this normal relationship between the pulmonary resistance and the lung volume is altered. Furthermore, the changes in the pulmonary resistance during expiration often do not follow those during inspiration.

The manner in which the pulmonary resistance–lung volume relationship is altered in bronchial asthma, pulmonary emphysema, pulmonary sarcoidosis, chronic pulmonary vascular congestion and other cardiopulmonary disorders has been studied. The type of alteration in the relationship between resistance and lung volume during both inspiration and expiration is quite specific for each disorder and appears to depend on the pathophysiology of the various diseases. Simultaneous measurement of pulmonary resistance to ventilation and lung volume may be useful clinically in differentiation between bronchial asthma and the so-called cardiac asthma.

Body Fluid and Electrolyte Composition in Primary Hyperaldosteronism

Aram V. Chobanian and William Hollander, Boston, Mass.

Total exchangeable sodium (Na^{24} space), potassium (K^{42} space), and extracellular fluid volume ($S^{35}O_4$ space) were measured in 11 patients with primary hyperaldosteronism. In contrast to matched normotensive controls or patients with uncomplicated essential or renal hypertension studied by us, the aldosterone group has shown significant increases in body sodium and extracellular fluid volume. Although similar degrees of subclinical sodium retention were observed in benign and malignant hypertension complicated by heart failure, the aldosterone group differed from all other hypertensive groups studied by a severe degree of body potassium depletion which was not necessarily reflected by the serum potassium levels.

The abnormalities in body fluids and electrolytes in 8 patients with aldosteronism studied 2 to 12 months following corrective adrenal surgery reverted to normal levels. In 3 of these 8 patients blood pressure decreased to normal, and in 4 others it decreased significantly although not to normal levels. Preoperative repletion of body potassium failed to relieve the hypertension.

In conclusion: (1) in contrast to other hypertensive states, the body electrolyte composition in patients with primary hyperaldosteronism is characterized by a significant increase in body sodium and a marked decrease in body potassium; (2) the hypertension of primary aldosteronism is generally relieved by corrective adrenal surgery; (3) the determination of exchangeable potassium may be of diagnostic use in suspected cases of hyperaldosteronism.

Cholesterol Synthesis in Human Blood Vessels

Aram V. Chobanian and William Hollander, Boston, Mass.

Recent radioisotopic studies in our laboratory have indicated that significant exchange takes place between serum and blood vessel cholesterol in human subjects. The present investigation was undertaken to determine whether any other mechanism might be involved in the accumulation of cholesterol in the arterial wall.

Segments of human arteries removed at the time of surgery for aortic vascular disease or for limb amputations have been incubated in media containing C^{14}-labeled precursors of cholesterol, C^{14} acetate and C^{14} mevalonic acid. The rate of formation of C^{14}-labeled sterols in the arterial wall has been followed over a 3- to 24-hour period. The results indicate that significant synthesis of cholesterol from both labeled precursors occurs in the human arterial wall studied in vitro. The sterol radioactivity does not appear confined to a single area, but is present in both the intima and the outer layers of the arteries studied.

In conclusion, significant synthesis of cholesterol occurs in the human arterial wall. The findings suggest that the accumulation of cholesterol in the blood vessels may result from both an exchange with serum cholesterol and a synthesis of cholesterol in the vessel wall.

Blood Formation and Destruction in Heart Failure

Robert B. Chodos, Syracuse, N. Y., William Chaffee, Orange, Conn., and Raymond Wells, Jr., Syracuse, N. Y.

The red cell volume, as well as plasma volume, may be increased in heart failure. In certain patients, red cell volume may decrease following compensation. Since the mechanism responsible for this decrease has not been demonstrated, studies were undertaken to determine whether the decrease is due to decreased formation or increased destruction of erythrocytes, or to a combination of these processes.

Red cell and plasma volumes were measured independently during failure and after compensation, employing radiochromium (or radiophosphorus) and T 1824, respectively. Erythropoiesis was estimated by radioiron turnover technics. Destruction of red cells was evaluated by radiochromium red cell survival and by estimation of fecal urobilinogen.

Red cell volume decreased significantly in 5 of 10 patients, plasma volume in 6 of 10, and total blood volume in 8 of 10. There was no evidence of increased blood destruction. Red cell survival was normal in all patients and there was no increase in fecal urobilinogen. During cardiac decompensation, the half time of plasma iron disappearance was rapid (0.33 to 1.15 hours) and plasma and red cell iron turnover were both consistently increased (43 to 182 mg./d.). After

compensation, the half time of plasma iron disappearance increased (1.0 to 2.0 hours) and plasma and red cell iron turnover both decreased strikingly. Control studies in normal subjects did not show significant changes in iron turnover.

These data indicate a definite decrease in iron turnover following compensation from heart failure. It is suggested that the mechanism responsible for any decrease in red cell volume is a decrease in erythropoiesis.

Circulatory Response to the Trauma of Surgery and Its Relationship to Chemical Homeostasis

George H. A. Clowes, Jr., Louis R. M. Del Guercio, and Jaroslaw Barwinsky, Cleveland, Ohio

To delineate what part is played by the circulatory system in the maintenance of homeostasis following the trauma of major surgery, the cardiac output was measured before, during, and after the operation in 60 patients. There were equal numbers of these who underwent pulmonary, cardiac, or intra-abdominal procedures. Simultaneous determinations of the oxygen consumption, the arterial blood gases, and plasma electrolytes were obtained.

A definite pattern of circulatory response to this trauma appeared to be present in those patients who made uneventful recoveries. During the period of anesthesia and operation, a reduction of the cardiac index to a mean of 2.1 ± 0.3 L./M²/min. occurred. This was accompanied by an elevation of both the central venous pressure and the total peripheral vascular resistance, and a metabolic acidosis. At the time of awakening when endotracheal extubation took place, a rapid increase of the mean cardiac index to 3.6 ± 0.5 L./M²/min. was found. In the cardiac patients this was particularly dramatic, for their mean preoperative index was 2.1 L./M²/min. In the immediate postoperative period, a slight depression again took place in many with a recurrence of acidosis, both metabolic and respiratory. Thereafter, during the first week the resting cardiac output remained above normal in the patients who underwent thoracotomy. By contrast, those in whom laparotomy had been performed exhibited normal or slightly subnormal cardiac indexes. No correlation appears to be present between oxygen consumption and cardiac output in the postoperative period.

From these findings it may be concluded that no great demand is made upon the heart in order to recover from major surgical trauma. However, death ensued in a state of profound uncompensated acidosis in 6 patients who proved unable to elevate their cardiac outputs postoperatively to values near the normal basal levels.

Postventriculotomy Right Bundle-branch Block: Its Etiology

C. Joan Coggin, Ellsworth E. Wareham, and Ronald H. Selvester, Los Angeles, Calif.

Atypical right bundle-branch block following the repair of ventricular septal defect has always been attributed to placement of the sutures in the ventricular septum. This report presents data which we believe suggest that the conduction defect in these cases is the result of the ventriculotomy itself and is not due to the sutures.

One hundred consecutive patients undergoing open heart surgery with the aid of extracorporeal circulation provide the basis of this study. Forty-five patients had ventriculotomy with preoperative electrocardiograms and vectorcardiograms with no evidence of right bundle-branch block. The postoperative electrocardiogram and vectorcardiogram of each demonstrated an atypical right bundle-branch block.

Continuous monitoring of the electrocardiogram during surgery showed that this pattern appeared at the precise moment of incision of the right ventricle. This occurred before the sutures were placed. In several instances continuous monitoring of the vectorcardiogram was done to further substantiate this time relationship.

These findings were confirmed experimentally with healthy mongrel dogs using extracorporeal circulation. A ventriculotomy only was done and the septum left untouched. In all cases, atypical right bundle-branch-block pattern developed at the time the right ventricle was incised.

These studies strongly suggest that the postventriculotomy right bundle-branch-block pattern that has been described is not secondary to the placement of sutures in the interventricular septum, but is secondary to the ventriculotomy itself.

Further Studies on the Phenothiazine Derivatives in Experimental Shock

Kenneth Collins and Joel G. Brunson, Jackson, Miss.

Albino rats of the Sprague-Dawley strain were subjected to a 30-minute period of rotational shock in a modified Noble-Collip drum, in conjunction with an intraperitoneal injection of 1 of 3 phenothiazine derivatives. A total of 276 rats was used, of which 72 served as controls. Of these, 69 (97 per cent) died within 24 hours following the period of rotation. Of 60 animals given 1 of the drugs simultaneously with the onset of drum rotation, 55 (91 per cent) survived longer than 24 hours, but no significant difference was noted between individual drugs. However, when the drugs were given after a period of rotation of 15 mi-

es, and rotation continued for an additional 15 inutes, only 1 of 24 animals given WY 2132 or 22-2D survived, but 8 of 12 animals given WY 45 survived longer than 24 hours. On the con- ary, when the drugs were given 1 hour prior to um rotation, only 4 of 12 animals given WY 45 survived, but 21 of 24 given WY 2132 or 22-2D survived for more than 24 hours. Of e total group of 204 experimental animals given of the drugs at varied intervals before or during e period of drum rotation, 127, or 62 per cent, rvived longer than 24 hours. The data confirm revious studies in rabbits on the efficacy of the henothiazine derivatives in preventing death in rum-shocked animals, but indicate that functional ifferences exist in this group of drugs although heir basic chemical structure is similar.

Abdominal Complications of Anticoagulant Therapy

W. Ford Connell and George A. Mayer, Kingston, Ontario, Canada

In the course of anticoagulant treatment of 1,971 inpatients and 407 outpatients at the Anticoagulant Clinic of the Kingston General Hospital, we encountered 16 patients with an acute abdominal syndrome. Clinical symptoms consisted of diffuse abdominal pain and distention, usually of rapid onset; muscular rigidity was not a feature. Bowel sounds were absent. In 4 patients, the simulation of an acute "surgical" abdomen was so marked that immediate surgery was considered. Four patients exhibited melena or hematuria at onset; 4 others developed these signs within 12 to 36 hours. In 6 patients no overt bleeding was observed. In 13 patients there was a moderate fall in hematocrit. In no case was laparotomy performed. In every instance the authors' Standard Clotting Time was found to be elevated markedly beyond the upper limit of the therapeutic range. Administration of vitamin K_1 oxide or simple readjustment of anticoagulant dosage was uniformly successful in producing a marked improvement in the clinical picture within 24 hours. In 13 cases anticoagulant therapy was restarted and has been continued for months or years without further abdominal symptoms.

erum Lipids in Men Receiving High Cholesterol and Cholesterol-free Diets

William E. Connor, Robert E. Hodges, and Roerta Bleiler, Iowa City, Iowa

Previous studies suggested that 1,700 to 4,800 g. of dietary cholesterol provided as egg yolk roduceed marked increases in serum cholesterol. ecently the authors gave cholesterol as egg yolk amounts similar to American intakes and compared this with crystalline cholesterol.

Six healthy men, aged 40 to 49, were given a normal diet 1 week and subsequently formulas, each providing 3,000 calories, 70 Gm. protein and 133 Gm. fat. The fat was a vegetable oil mixture with saturated fatty acid composition similar to egg yolk. The iodine numbers for all periods were 84 to 86. The experimental periods of 3 weeks each were: (1) cholesterol-free; (2) egg yolk providing 475, 950, and 1,425 mg. of cholesterol for respective pairs of men; (3) cholesterol-free; and (4) crystalline cholesterol, 1,200, 2,400, or 3,600 mg. During the egg yolk feeding, 11 to 33 Gm. of the total fat was derived from egg yolk.

The mean serum cholesterol decreased 57 mg. per cent ($p < 0.01$) during the first cholesterol-free period (1). The addition of egg yolk (2) led to an increase of 68 mg. per cent ($p < 0.001$). No differences occurred among the 3 cholesterol intakes. With the second cholesterol-free formula (3), the serum cholesterol decreased 55 mg. per cent ($p < 0.001$). Serum phospholipids varied with the serum cholesterol. In period 4, crystalline cholesterol increased the serum cholesterol 18 mg. per cent.

In diets equivalent in amounts and composition of fat, the addition or subtraction of moderate amounts of cholesterol as egg yolk caused significant changes in serum cholesterol concentrations.

Effect of Bretylium Tosylate, A Sympathetic Blocking Agent, on the Circulation

James Conway, Ann Arbor, Mich.*

The parenteral administration of bretylium tosylate produces an increase in blood flow to the hands and feet with little change in forearm flow. There is a slight fall in heart rate and blood pressure in most recumbent hypertensive subjects and a similar change in cardiac output. In approximately 15 per cent of hypertensive patients, however, an unexpectedly large reduction in recumbent blood pressure is seen in the recumbent subject.

Oral therapy with bretylium requires a dose of 600 to 3,200 mg./day. This results in an average fall in blood pressure of 11/13 mm. Hg, recumbent and 32/22 standing. The side effects are chiefly due to postural hypotension. Individual titration of dosage is required. Tolerance develops in the first month of administration. This can usually be overcome by increasing the dosage.

Are Present-day Practices in Recommending Work for Persons with Heart Disease Correct?

W. Leigh Cook and William B. Tuttle, Pittsburgh, Pa.

This study attempts to assess the validity of present notions concerning the effect of work on persons with heart disease. Current practices of

formulating "work prescriptions" based upon personal experience and empiricism are utilized in all cardiac work evaluation clinics. These methods have remained unchallenged with the assumption that they are sound despite the lack of uniformity and the absence of proof of the long-term effect of work recommendations on the persons under study. A study of the survival of 611 persons with arteriosclerotic or rheumatic heart disease followed for periods up to 8 years is reported in relation to the patients' compliance with a cardiac work evaluation unit's work prescriptions. The data are presented in the form of actuarial tables and exponential survival curves. The following conclusions seem warranted:

1. In both diseases, longevity was greatest in the group of patients which complied with the clinic's recommendations for work.

2. In patients with arteriosclerotic heart disease, survival was shortened in those who exceeded the recommended total work activity as compared to those who complied with recommendations or those who did less than advised.

3. In patients with rheumatic heart disease, a similar unfavorable survival rate was observed for those exceeding the work recommendations as compared with those complying. The magnitude of the difference between those exceeding and complying was considerably less than observed in patients with arteriosclerotic heart disease.

Cholesterol Biosynthesis Inhibition by Triparanol (MER-29)

Elmer E. Cooper, San Antonio, Texas

Among the therapeutic attempts to lower serum cholesterol, inhibition of biosynthesis at the liver level using MER-29 has been investigated.

Thirty-six subjects with and without atherosclerotic disease have been given this drug from 1 to 5 months at an oral dosage of 250 to 750 mg. per day. The average control was determined from 3 separate tests taken at weekly intervals. Follow-ups during medication were taken every 2 weeks. Analyses were done by the same technician, using the Bloor colorimetric method. There were no dietary restrictions.

Thirty-three of the 36 subjects had an appreciable reduction of serum cholesterol ranging from 26 to 122 mg. per cent or 8 to 43 per cent of control values. Depressions in cholesterol occurred within 1 week and progressed to their maximum drops in 4 to 6 weeks. These lowered levels were maintained throughout the study with only slight variations. Within 2 weeks after medication was discontinued, the cholesterol levels rose to control values. Repeat courses of medication reproduced similar lowering of cholesterol levels. No toxic effects were observed in hematopoietic cardiovascular or renal systems. Serum bilirubins, urobilinogens, alkaline phosphatases, and transaminases (SGOT) were all normal. Cooperation and tolerance were excellent. In 1 instance, there was a evanescent erythematous rash.

Treatment of Hypercholesterolemia with Thyroid Analogues in Patients with Coronary Artery Disease

Eliot Corday, David W. Irving, and Henry Jaffe, Los Angeles, Calif.

The hypocholesterolemic action of the thyroid analogues tetraiodothyroformic acid (T_4F), triiodothyropropionic acid, and sodium dextrothyroxin have been studied in 56 patients for a period of 1 year. Most of these patients were previously made hypothyroid with I^{131} because of severe coronary artery disease and all had hypercholesterolemia. The patients were unable to tolerate normal doses of thyroid medication because of adverse metabolic and adrenergic effects. Serum cholesterol levels were obtained every 2 weeks. Placebos were first administered for a 2- to 12-week period, then the thyroid analogue was given and the patients observed for a further 12-month period. The drug was stopped and restarted several times to prove that the reduction was due to the agent.

The thyroid analogues showed a marked hypocholesterolemic effect. In the T_4F series of 26 patients, the average control cholesterol was 372 mg. per cent and the average reduction was 148 mg. per cent (a drop of 33 per cent). Equally effective results were noted in the triiodothyropropionic acid group.

These thyroid analogues have minimum metabolic or adrenergic effects and are effective in lowering serum cholesterol levels in brittle coronary patients.

Electrocardiographic Changes in Carbon Monoxide Poisoning

Richard S. Cosby and R. Michel Bergeron, Pasadena, Calif.

In spite of extensive experimental studies, the precise role of carbon monoxide and its effect on the myocardium in man has not been entirely clarified. Changes simulating coronary artery disease with anoxia have been reported along with focal abnormalities more suggestive of myocarditis. The present study presents further electrocardiographic evidence and attempts to formulate a thesis of the type of myocardial changes encountered.

One hundred and twenty-three cases of carbon monoxide poisoning from the records of the Los Angeles County General Hospital and the Hun-

ington Memorial Hospital were examined. Ten patients showed electrocardiographic changes of significance. Of these, 2 patients died and the pathologic findings are reported. The electrocardiographic findings are predominantly coronary in type with depression of the ST-T segment and inversion of the T waves. However, no instances were found of reciprocal S-T deviation nor of the appearance of abnormal Q waves. In 1 patient, ST-T changes persisted long after the patient was clinically improved and the patient developed angina pectoris.

The clinical findings, carbon monoxide levels, and clinical course of this series are reviewed. The pathophysiology of the changes is presumably due to 2 factors: the severe initial anoxia producing ST-T changes, arrhythmias, and death, and subacute changes which appear more like those of subendocardial ischemia. The evidence is against either focal "myocarditis" or coronary artery block.

Mechanism of the Generation of the Third and Fourth Heart Sounds

Lamar Crevasse, W. Jape Taylor, Myron W. Wheat, and Richard F. Leeds, Gainesville, Fla.

Technical difficulties have prevented a precise correlation of intracardiac pressure events and sound production in relation to the third and fourth heart sounds, and results have been controversial in the past. To circumvent these difficulties, intracardiac sound and pressure events were recorded simultaneously from atrium and ventricle through an 18-gage needle and Statham transducer. This was complemented by the conventional external, epicardial, and intracardiac crystal microphones in open and closed chest dogs and humans.

Fourth Heart Sound: During atrial contraction, subaudible vibrations of the frequency 15 to 25 c.p.s. were recorded simultaneously with the peak of the atrial pressure wave within the atria. Following by .01 to .02 seconds after the peak of atrial contraction, audible sound of the frequency 25 to 75 c.p.s. was recorded within the ventricles and coincided with the pressure inflection on the simultaneous intraventricular tracing. Atrial pressure always exceeded ventricular pressure during these events. Epicardial phonocardiograms and direct observation of the ventricular wall during complete heart block demonstrated ventricular muscular vibrations in the audible range following atrial contraction per se.

Third Heart Sound: This sound, recorded from within the ventricle, occurred .10 to .20 seconds after aortic valve closure at a point coinciding with rapid ventricular filling. The relationships between atrial and ventricular pressures consistently demonstrated that atrial pressure exceeds ventricular pressure when this sound is present. The presence and intensity of the sound were, in part, a function of the magnitude of the atrial-ventricular pressure differential. No significant vibrations were recorded from within the atria. Epicardial phonocardiograms again demonstrated audible ventricular vibrations during these relationships.

The rapid infusion of saline in dogs with normal A-V conduction induced separation of the fourth heart sound from the initial component of the first heart sound with the same temporal relationships between atrial and ventricular pressures noted above. The third and fourth sounds first appeared or became exaggerated following rapid infusion with saline. The atrial-ventricular pressure gradient increased.

These observations demonstrate that the audible third and fourth sounds have a common origin in the ventricles. The audible fourth heart sound follows atrial contraction and occurs at a time when atrial pressure exceeds ventricular pressure. It is related to sudden augmentation of late diastolic ventricular filling with resultant audible ventricular vibrations. Similarly, the third heart sound occurs at a time when the A-V valves are open during early rapid diastolic filling with observable and recordable ventricular muscular vibrations. These sounds may be generated in either ventricle.

Altered Response to Protoveratrine and Sodium Cyanide after Bilateral Glossopharyngeal Nerve Section in Man

James H. Currens, H. Thomas Ballantine, and Mandel E. Cohen, Boston, Mass.

A male patient was studied before and after the glossopharyngeal (ninth) nerves were sectioned intracranially. The left nerve was sectioned and 2 weeks later the right nerve was cut to relieve neck pain caused by cancer of the throat. The following observations were made:

1. Blood pressure and pulse rate were determined for 30 minutes before and after the intravenous injection of protoveratrine A and B (0.12 mg.), twice before and after the operations. Average blood pressure change before operations was from 12.6/6.5 to 8.8/5.0 cm., and after operations from 13.2/7.3 to 11.8/7.0 cm. Pulse rate changed from 86 to 81.2 before and 100 to 98.1 after operations.

2. Sodium cyanide (6 mg.) was given by intravenous injection once before, twice after the right nerve was cut, and 3 times after both nerves were cut. Respiratory stimulation with increase in rate and depth of breathing and increase in pulse rate occurred each time before both nerves were cut. No increase in respiratory rate or depth or in-

crease in pulse rate was noted after the second operation when sodium cyanide was given in dosage to 8 mg. on 3 occasions.

One previous patient failed to respond to protoveratrine and sodium cyanide by intravenous injection after bilateral glossopharyngeal nerve section. In 2 humans studied, the glossopharyngeal nerves are essential for the stimulating effect of cyanide upon respiration and circulation, and for at least part of the action of protoveratrine on blood pressure.

Surgical Studies of the Lymphatics

Callisto Danese and John M. Howard, Philadelphia, Pa.

A simple technic has been developed in this laboratory for lymphangiography. A radiopaque medium is injected beneath the skin (dog) of the paw. A blood pressure cuff is inflated around the paw in an effort to increase tissue pressure. Within 3 minutes thereafter, a roentgenogram outlines the lymphatics and lymph nodes of the extremity.

In a study of the possibility of reparative surgery of the lymphatics, several procedures have been evaluated on a total of 30 dogs. It has tentatively been observed that: (1) hemisection and resuture of a lymph node and section and reinsertion of afferent or efferent vessels into a lymph node heal without affecting the lymph-carrying capacity as measured by lymphangiography; (2) an autotransplanted lymph node deprived of its own blood supply undergoes fibrosis with disappearance of parenchymal lymphatic tissue, but when sutured with another lymph node (half a node transplanted and sutured to another half lymph node) it is able to obtain its sustaining nutrient from the lymph or from the adjacent half node.

Further observation and studies are in process in order to extend these studies. The other procedures have been performed on a total of 20 dogs in a study of lymphatic regeneration. 1. Circumferential section and resuture of the soft tissues of the thigh at its middle third except for the superficial femoral artery, vein and nerves. Progressive edema develops and begins subsiding after 2 weeks. It disappears almost completely within 3 weeks. Lymphangiograms show regenerated lymphatics, more numerous and larger than before surgery. 2. The same operation plus segmental resection of lymphatics from the popliteal lymph node to the inguinal area. Presently, after intervals ranging from 3 to 5 weeks postoperatively, these dogs still have an enormous edema.

Long-term Results of Surgery for Mitral Insufficiency

Julio C. Davila, James L. Harrison, Alberto E. Edwards, A. Jane Fritz, and Robert P. Glover, Philadelphia, Pa.

During the past 5½ years, 75 patients with severe degrees of mitral insufficiency were operated. Correction was accomplished by circumferential suture of the mitral annulus. Thirty-five of these patients are living 13 months to 65 months after surgery. Twenty of these have had postoperative hemodynamic studies from 8 to 40 months after operation. At this writing 28 patients (80 per cent of the surviving group) have shown significant improvement.

The present status of the surviving patients is presented utilizing clinical and hemodynamic data. The factors influencing operative and late mortality are discussed. A group of 15 patients with advanced mitral regurgitation who did not have corrective surgery is presented and compared with the operated cases.

Criteria which have evolved in the course of this experience applying to selection of patients for surgery as well as to choice of operation are presented. Adherence to these principles has led to marked reduction in operative risk (no operative deaths in the last 18 consecutive cases) and to gratifying long-term results.

Normal and Pathologic Mechanics of Cardiac Valves: With Considerations Toward the Development of Prosthetics

Julio C. Davila, Trevelyan E. Palmer, and Robert P. Glover, Philadelphia, Pa.

This study is concerned with the features of normal and pathologic mechanics of the mitral and aortic valves which pertain specifically to the criteria which acceptable cardiac valvular prosthesis must fulfill. Particular attention is placed on the effects of changes in morphology, pliability and motion or displacement of the leaflets of the atrioventricular and semilunar valves and on the role of the chordae tendineae and the participation of the ventricular myocardium in valvular motion in the atrioventricular valves. Several types of prosthetic valves constructed of various materials were used to illustrate certain requirements as to design, physical properties of material and possible methods of fixation.

The report is based on studies, using the pulse duplicator, on normal and diseased human and animal hearts in which the action of the natural valves as well as of artificial ones was observed. Animal experiments to evaluate the suitability of certain materials are used to illustrate pertinent points.

Surgical Considerations of Occlusive Disease of the Great Vessels Arising from the Aortic Arch

Michael E. De Bakey, E. Stanley Crawford, Denton A. Cooley, George C. Morris, Jr., and Walter S. Henly, Houston, Texas*

Thrombo-obliterative disease of the great vessels arising from the aortic arch is a clinical entity sometimes called Takayasu's disease, aortic arch syndrome, pulseless disease, reverse coarctation, or Martorell's syndrome. These terminologic variations along with certain reported concepts of the occlusive process have caused confusion regarding the nature of the disease process. It is significant that some proposed concepts of the pathogenesis of the disease preclude application of effective surgical treatment to restore normal circulation. Accordingly, we are reporting our observations derived from analysis of 50 cases using surgical treatment to restore normal circulation.

This study supports the concept of the segmental nature of the occlusive process and its tendency to assume certain well defined patterns despite considerable variation in its pathologic features. Although the occlusive process may be extensive and the vessels may be involved in an inflammatory process probably incited by superimposed thrombosis, the underlying etiologic factor in most cases appears to be atherosclerosis. Clinical manifestations, including age and sex incidence, may be correlated with certain pathologic features of the disease. It is also significant that some patients had associated segmental occlusive disease in other parts of the major arterial tree, emphasizing the emerging clinical patterns of multiple segmental atherosclerotic occlusive disease. Results of surgical treatment have been gratifying, and restoration of normal circulation in the distal arterial bed was achieved in all cases, including those associated with other occlusive lesions. Application of several surgical procedures, singly or combined in accordance with various patterns of occlusion, was studied.

Effect of Reserpine on the Altered Hemodynamics of Hyperthyroidism

William J. deGroot, James J. Leonard, Hyman W. Paley, John E. Johnson, and James V. Warren, Galveston, Texas

The increased cardiac output associated with hyperthyroidism has been reported to result from an increased heart rate without change in stroke volume. Recent studies using rauwolfia alkaloids in this disease have demonstrated a consistent pulse slowing along with other changes which suggest slowing of the circulation. To test this assumption, 8 untreated hyperthyroid patients (average age 29) were hospitalized and their hemodynamic status evaluated 4 days after admission and again after treatment with 10 mg. of intramuscular reserpine daily for 3 days.

Cardiac index (mean 5.82 L.) and heart rate (mean 102) were above normal in all patients. Stroke volume was also increased, but not significantly (95 ± 20 cc.). However, when this parameter was related to body surface area, a statistically significant change was noted (57 ± 10 cc. $p < 0.01$) when compared to normal (45 ± 6 cc.). After reserpine, despite an unequivocal slowing of the heart rate (85 ± 11 $p < 0.01$), the cardiac index was unchanged (mean 6.20 L.). Thus, the pulse rate decrement effected a major increase in stroke volume (120 ± 34 cc. $p < 0.05$).

Although pulse slowing after reserpine administration has been confirmed, this phenomenon is not associated with a decrease in cardiac output. Rather, the excessive flow of hyperthyroidism is now maintained by a considerably augmented stroke volume. This would indicate that the calculated effective ventricular "work" per stroke is increased although other aspects of work and efficiency may be unchanged. Another interesting result of these studies is the suggestive evidence that basal stroke volume of untreated hyperthyroid patients may be above normal.

Recurrent Stenosis of the Mitral Valve

Jose R. De Jesus, Jr., Gerald M. Breneman, John W. Keyes, and Conrad R. Lam, Detroit, Mich.

Forty-three patients were reoperated for suspected restenosis of the mitral valve. Thirty-five of the group were from a series of 672 mitral commissurotomies performed at our clinic, while 8 patients had the initial operation elsewhere.

Severe deformity, often with subvalvular involvement and calcification, results in an inadequate commissurotomy and the early recurrence of symptoms in cases of "false" restenosis. True restenosis may follow active rheumatic carditis or subacute bacterial endocarditis.

Restenosis is suspected in a patient who develops recurrent symptoms following a variable period of improvement after mitral commissurotomy. The interval between operations was 1 to 8 years, with an average of 4 years. A few of the patients showed signs of more advanced mitral valve disease and pulmonary hypertension at the time of second operation. Right ventricular hypertrophy was reflected in the electrocardiograms in 13 cases (30 per cent) and on x-rays in 29 cases (68 per cent). Twenty patients (47 per cent) had calcified mitral valves on fluoroscopic examination.

Cardiac catheterization was done in 20 cases: to assess the degree of possible mitral incompetency in 14 patients who had an apical systolic murmur in addition to the murmur of mitral stenosis, and in 6 cases to rule out the presence of significant pulmonary or additional myocardial disease. Catheterization is not deemed necessary in those cases presenting typical clinical features.

There was an operative mortality of 10 patients

(23 per cent), indicative of the more severe pathophysiologic changes in these individuals. Thirty-three patients were judged to have a good result, although 3 died later. Direct-vision commissurotomy with the pump oxygenator was used 4 times, and is being considered in every case at present.

Pressure Gradients as a Means of Determining the Degree of Renal Artery Stenosis

John R. Derrick, Galveston, Texas

Experimental Background:

Varying degrees of constriction of the femoral artery and aorta were produced in 15 dogs weighing between 8 and 16 Kg. The differences in sizes of the experimental animals permitted one to change, over a wide range, the degree of constriction of the cross-sectional area of individual arteries. Pressure gradients were then determined immediately, and after a period of 2 to 6 months. During each determination the blood pressure was elevated and depressed to determine the significance of varying degrees of blood pressure on the pressure gradient across the constricted area.

In each instance, by varying the animals' blood pressure, it was found that one could change the gradient across the stenosed area. The degree of gradient would become much greater at lower blood pressures than at extremely high blood pressures; however, when the pressure dropped below 50 to 60 mm. Hg there was again a narrowing of the gradient.

Clinical Experience:

Simultaneous pressure determinations of the renal arteries and aorta were done in 10 patients as the blood pressure was varied, using angiotensin to elevate the pressure, and a hypotensive agent to lower the pressure. Clinical data substantiated the findings in the experimental laboratory.

Studies of the Relation Between the In Vivo Antithrombotic and In Vitro Anticoagulant Actions of Dicumarol

Daniel Deykin, Stanford Wessler, and Stanley M. Reimer, Boston, Mass.

Experimental evidence for the antithrombotic activity of coumarin-type compounds is scanty and the relation of this activity to drug-induced depression of specific clotting factors remains obscure. These problems were explored with the technic of serum-induced thrombosis, using the systemic infusion of thrombin-free serum to induce massive thrombosis through activation of the "intrinsic" clotting system (in the absence of tissue thromboplastin). In this study, a quantitative bio-assay of the serum thrombotic accelerator (STA) activity of canine serum was used as a measure of in vivo thrombosis. Nine dogs received dicumarol in doses adequate to maintain the 1-stage prothrombic activity at less than 15 per cent of control values for 3 to 48 days; 3 dogs served as controls. Serial in vivo assays of STA activity and in vitro assays of clotting Factors II (prothrombin), VII (convertin), IX (PTC), and X (Stuart) were followed in all animals. A statistically significant antithrombotic effect was observed in 8 of the 9 treated animals without causing hemorrhage. This antithrombotic effect lagged days to weeks behind the anticoagulant effect and was independent of the depression of any clotting factor, singly or in combination, known to be affected by dicumarol.

This is considered to be the first experimental demonstration of an in vivo antithrombotic action of dicumarol mediated through the intrinsic clotting system. The data also suggest that dicumarol may exert this antithrombotic action by depressing a hitherto uncharacterized coagulation moiety.

Intravenous I^{131} Triolein Tolerance Curves in Patients with Diabetes Mellitus and Myocardial Infarction

Edward R. Dickstein, Leonard J. Feinberg, Samuel Bellet, and Herschel Sandberg, Philadelphia, Pa.

Previous studies have demonstrated that oral I^{131} triolein tolerance curves in patients with coronary artery disease and diabetes mellitus differ significantly from those of normal controls. The radioactivity in the whole blood and its circulating lipoprotein fraction is elevated in these conditions as compared to that found in normal controls. In order to evaluate the relative importance of absorption in producing these effects, this metabolic aspect has been bypassed by using the intravenous route for the administration of the labeled triolein. Twenty-six subjects were employed in this study: 10 with diabetes mellitus; 6 with myocardial infarction; and 10 served as a control group.

The I^{131} triolein, freshly emulsified and sterilized by pressure filtration, was administered intravenously to these individuals and serial blood samples were drawn in rapid succession for the first 10 minutes and less frequently thereafter for 3 hours. Twenty-four-hour samples were also obtained. The radioactivity in the whole blood and its circulating lipoprotein fraction (determined by precipitation with trichloracetic acid) was evaluated. It was found that 6 of the 10 diabetic subjects displayed a delay in the clearance of lipid from the blood stream. No significant difference was found between the control population and the subjects with myocardial infarction. No correlation could be drawn between the delay in the clearance of radioactivity in the diabetic subjects and parameters

such as serum cholesterol, daily insulin dosage, age, weight, or sex.

Observations on the Hemodynamics of Severe Aortic Insufficiency in Man

Harold T. Dodge, Harold Sandler, and Thomas Evans, Seattle, Wash.

Studies of left ventricular (LV) volume changes with observations of aortic, LV and left atrial (LA) pressures in a subject with severe aortic insufficiency (AI) provide a better understanding of the hemodynamics of severe AI. LV chamber volumes were calculated from biplane angiocardiograms recorded at 4 films per second and timed with respect to the electrocardiogram and arterial pressure. Calculated LV volumes were plotted with respect to time of cardiac cycle and a LV volume loop constructed. LV volume changes were related to LV, aortic and LA pressures recorded just prior to angiocardiography and confirmed by recordings at surgery. Marked elevation of LV end-diastolic volume (444 cc.) was present with a LV stroke volume of 209 cc., forward stroke volume of 48 cc. (Fick and dye-dilution technics), regurgitation of 161 cc./beat. LV and LA pressure relationships permitted LV filling for only 0.19 seconds of diastole (42 per cent of diastole). 0.25 seconds after onset of diastole, LV pressure exceeded LA pressure (11.5 mm. Hg gradient) and equilibrated with aortic pressure by 0.350 seconds (60 mm. Hg), falling gradually with aortic diastolic pressure.

These studies demonstrate the large volume of regurgitant flow, shortening of LA to LV filling period, a later diastolic period of aortic to LV filling and absence of further LV filling with equilibration of aortic and LV diastolic pressures. These observations help to explain the rising systemic arterial diastolic pressure, reversed LV to LA diastolic pressure gradient and demonstrate the importance of heart rate on forward flow, as reported by others, in subjects with severe AI.

Nodal Tachycardia: Etiology and Therapy

Leonard S. Dreifus, Giampiero Bartolucci, and William Likoff, Philadelphia, Pa.

Fifty-seven nodal arrhythmias were encountered in 11,000 consecutive records. All cases were excluded in which the acceleration of the nodal pacemaker was only transitory. Forty-one cases represented nonparoxysmal A-V nodal tachycardia and 16 other patients demonstrated a passive nodal mechanism. Of the group with nonparoxysmal A-V nodal tachycardia, 40 per cent was due to digitalis excess, another 30 per cent secondary to trauma engendered by intracardiac surgery, and the remainder of the cases were associated with posterior wall myocardial infarction, acute rheumatic fever, and myocarditis. Passive nodal mechanisms were invariably associated with atrial fibrillation with a high grade A-V heart block, and were secondary to digitalis excess. Omission of digitalis medication was usually sufficient to terminate this mechanism.

Surgically induced nodal tachycardia lasted from 1 to 5 days and converted to the preoperative mechanism in almost all cases. However, if digitalis was discontinued, a rapid atrial mechanism invariably ensued. Digitalis-engendered nodal tachycardias were not associated with hypopotassemia, although almost all cases responded to potassium infusion. In 6 cases, the rhythm was terminated by pronestyl. In 1 case of idiopathic myocardial hypertrophy, the nodal tachycardia could not be terminated, and the patient was discharged with this mechanism.

Rapid nodal mechanisms associated with acute rheumatic fever and posterior wall myocardial infarction usually regressed spontaneously, and did not require treatment.

Regularization and slowing of a previous atrial fibrillation suggested a passive nodal rhythm. Acceleration of a previous sinus mechanism, with or without "early" or "late" ventricular systoles (capture beats), indicated the development of nonparoxysmal A-V nodal tachycardia. Potassium and pronestyl proved most effective in the termination of the digitalis-induced nodal rhythms.

Intravascular Volume as a Determinant of Arterial Pressure and Sympathetic Vasomotor Tone

Harriet Dustan and Hideo Takagi, Cleveland, Ohio

In hypertensive patients, chlorothiazide causes increased responsiveness to ganglioplegics and decreased responsiveness to norepinephrine. These effects seem due to augmented sympathetic vasomotor tone resulting from decrease of intravascular volume; natriuresis seems important only through causing negative water balance.

To investigate further these factors, anesthetized normotensive rats were made hyponatremic, hypovolemic and hypotensive by intraperitoneal injection of 5 per cent glucose solution (15 ml./100 Gm.). After hypotension became established, plasma volume was restored in groups of rats either by 5 per cent salt-free albumin (0.9 ml./100 Gm.), hypertonic saline (1.2 mEq./100 Gm.) or isotonic saline (4.8 ml./100 Gm.). Arterial pressure (BP) was recorded continuously; estimates of vasomotor tone were obtained from BP responses to norepinephrine and serotonin. Similar experiments were done following pentolinium administration.

Intraperitoneal glucose decreased BP 30 per cent, plasma sodium 22 per cent, and increased hematocrit 33 per cent. Decreased responses to norepinephrine and prolonged depressor responses to serotonin suggested increased sympathetic vasomotor activity.

Both albumin and hypertonic saline returned BP to control levels and lowered hematocrit to less than control values; plasma sodium was 112 and 143 mEq./L., respectively. Isotonic saline was less effective in restoring BP and hematocrit; plasma sodium was 126 mEq./L. Norepinephrine responses were greater than control and serotonin was no longer depressor, suggesting decrease of sympathetic outflow. Pentolinium abolished or reduced changes in drug responses caused by hypotension and subsequent restoration of plasma volume.

These results show that BP and vasomotor tone depend on the magnitude of intravascular volume rather than body sodium content.

Clinical Experience with a New Antihypertensive Agent —Guanethidine

John T. Eagan and Edward S. Orgain, Durham, N. C.

Guanethidine, a new antihypertensive compound thought to act by blocking the release of transmitter substances from sympathetic nerve terminals, has been evaluated in a series of 37 outpatients suffering from primary hypertension. Classified according to grade severity of hypertension (Page), there were 4 mild, 20 moderate, 9 severe, and 4 malignant.

Guanethidine was administered alone, in oral doses ranging from 10 mg. to 400 mg. per day (average 73 mg.), in 2 to 4 divided doses over an average period of 19 weeks.

Nine patients (24 per cent) experienced a recumbent fall in mean blood pressure greater than 20 mm. Hg, while 22 patients (59 per cent) experienced a similar fall in standing blood pressure, indicating the greater postural effect of the drug. Effective responses were noted for each grade of hypertension and occurred over a wide range of drug dosage.

Over one half of the patients experienced mild side effects which, in decreasing order of frequency, were dizziness due to postural hypotension, diarrhea, fatigue, abdominal pain, impotence, abdominal "bloating," and nausea. Side effects could be alleviated by reduction in dosage. No toxic effects were noted upon repeated physical and laboratory examinations.

Guanethidine is a useful drug for the treatment of severe hypertensive vascular disease. All patients, irrespective of severity of hypertension, should be started on low doses of the drug. Increments in dosage should be made slowly, because of the wide variation in individual response.

Spatial Vectorcardiogram Geometrically Derived from Clinical Electrocardiographic Leads: Validation and Clinical Application

George Eastman, Pittsburgh, Pa.

Despite its self-evident value in cardiologic research and teaching, the vectorcardiographic technic has not had wide general application because of technical problems in oscilloscopic recording. A possible substitute method, that of geometric derivation of cardiac vector patterns, has always previously required tracing magnification in time and magnitude, special electrode placements or multichannel recording apparatus. Seeking the widest possible applicability to current or previously recorded electrocardiograms, we have studied a method of geometric derivation of the 3 cube system vector loops from 3 routine clinical scalar electrocardiographic leads, sequentially recorded, normally timed and standardized.

From these lead tracings, I, aV_F and V_1, there are determined groups of 7 vector determinant values. These, the P and T wave algebraic magnitudes, the initial and terminal movement directions, and the mean initial, mean entire and mean terminal QRS vector magnitudes, are then paired and plotted on rectangular coordinates. They yield sets of 3 mutually perpendicular QRS vector loops and T and P vector arrows.

Comparison between these derived loops and electronically recorded ones shows good agreement both in the normal and the diseased heart. Abnormalities of relative ventricular mass can be shown, as can discordant repolarization pathways and injury current effects in focal myocardial lesions. Analysis of a series of 250 electrocardiograms, representing a cross section of both normal and pathologic tracings, has been made and statistical criteria for cardiac diagnosis by this method have been calculated.

Effects of Reduced Cardiac Sympathetic Tone on Myocardial Function

John W. Eckstein and A. W. Horsley, Iowa City, Iowa*

The ventricular responses to the increased filling pressure (right atrial mean pressure) produced by tilting into the head-down position were studied in 10 dogs lightly anesthetized with thiopental sodium and treated with gallamine triethiodide. Animals prepared in this fashion have highly responsive sympathetic nervous systems. Cardiac output was obtained from continuously recorded concentration curves of indocyanine green dye. Pressures were recorded from the systemic and pulmonary arteries and right atrium.

Before administration of a ganglionic blocking agent, there were no significant changes in heart rate, minute volume, stroke volume or external

work of either ventricle in response to increased atrial pressure.

After cardiac sympathetic tone was reduced by administration of a ganglionic blocking agent (trimethidinium), heart rate, minute volume, stroke volume and ventricular work fell. Restoration of atrial pressure caused significant increases in these functions, but the levels present before trimethidinium were not achieved. Restoration of the ventricular rate by pacing the atrium electrically caused no further increase in minute volume or work, but stroke volume and work fell appreciably.

It is suggested that the increased atrial pressure before trimethidinium causes no change in cardiac output or work because of reflex withdrawal of sympathetic tone to the myocardium and consequent shifting of the ventricular function curve to the right. The pharmacologically denervated heart with its rate controlled seems to operate on a low ventricular function curve and appears to increase its output only with an increase in filling pressure. Its behavior resembles that of a heart-lung preparation.

I^{131} Oral Triolein Tolerance Curves in Elderly Patients with Coronary Artery Disease

Jerry Edelman, Herschel Sandberg, Edward R. Dickstein, and Samuel Bellet, Philadelphia, Pa.

Earlier studies have demonstrated that middle-aged subjects with documented evidence of myocardial infarction metabolize orally administered I^{131} triolein in an abnormal manner. Following the ingestion of a labeled test meal, the radioactivity in the whole blood (WB) and its circulating lipoprotein fraction (TCA) reaches higher levels and remains elevated for at least 24 hours compared to those of a control population. In patients with diabetes mellitus, similar abnormalities were found, particularly in patients with atherosclerotic complications.

These abnormal curves failed to appear, however, in diabetics over 60 years of age. It was, therefore, decided to study oral I^{131} triolein tolerance curves in elderly individuals with coronary artery disease.

Twenty-five subjects with clinical and electrocardiographic evidence of coronary artery disease were utilized in this study. Ten were 60 years of age or older; 15 were under 60 years. The I^{131} triolein test meal was administered to these individuals and serial blood samples were drawn and analyzed for radioactivity in the whole blood (WB) and trichloracetic acid precipitable fraction (TCA). In several instances serum cholesterols and phospholipids were also determined.

The peak whole blood activity (WB), circulating lipoprotein activity (TCA) and fraction of total blood activity precipitable with trichloracetic acid (TCA/WB) were considerably higher in the younger subjects than in those over 60 years of age. The values of the latter were similar to normal controls. There was little difference between the groups 24 hours later, however. Impaired absorption in the older age group was believed to account for the observed differences.

Ten-year Status after Sympathectomy for Arteriosclerosis

Edward A. Edwards, Boston, Mass., and Chilton Crane, Brookline, Mass.

The status by the tenth postoperative year of 100 patients who underwent sympathectomy 10 to 19 years ago is reported. Twenty-seven patients were diabetic and 39 showed severe visceral disease when first seen. The initial limb problems were likewise quite fully representative in variety and severity of arteriosclerotic disease.

The survival of the patients during the 10 postoperative years illustrates the life history of arteriosclerosis. Diabetes casts a baleful influence on longevity, as well as on the postoperative result in the limb. A good result was associated with a better life expectancy. This represents a relationship between diffuse disease in the limb and arteriosclerosis in internal organs that has already been noted in the 5-year status previously reported.

Major amputations were occasioned mainly by the failure of the operation to correct the initial presenting problem, since amputations were rare after the first postoperative year.

There was no evidence of late reinnervation or of neurohumoral sensitivity of the limb. The few instances of late deterioration were always accompanied by objective evidence of new major arterial occlusion.

Recurrent Pulmonary Embolism as a Remediable Cause of Chronic Heart Failure

Edward A. Edwards, Lewis Dexter, and William C. Donahue, Boston, Mass.

This is a review of our experience with repeated pulmonary embolism which has caused chronic heart disease or precipitated or aggravated preexisting heart disease. Unless the disorder is recognized and treated definitively, the course leads inexorably to death. Diagnosis is difficult because the signs are mainly those of right or left heart failure, rather than typical pulmonary signs.

Since at least two thirds of the pulmonary arterial tree is probably already occluded when heart strain becomes manifest, treatment must be definitive. We have found anticoagulants to be ineffective in this situation. Vein ligation, with postoperative heparinization, has arrested the downhill

course of most patients, whether or not preoperative signs of venous thrombosis could be found.

Vein ligation may fail, however, unless attention is paid to the several variations of the femoral vein or the inferior vena cava, and a meticulous technic is employed. The variations significant for this thesis have been studied. In some of our patients, embolism continuing after ligation has been stopped after reoperation with division of a responsible collateral channel.

Management of Acute Instrumental Mitral Insufficiency

W. Sterling Edwards and Champ Lyons, Birmingham, Ala.

In a series of several hundred mitral valvulotomies in the past 10 years, 5 have sustained serious injury to valve leaflets with resultant acute insufficiency. Insufficiency was produced in 2 with digital manipulation, in 2 others with a guillotine knife, and in 1 with a transventricular dilator. Three of these 5 patients died, 2 after unsuccessful attempts to suture the lacerated leaflet with extracorporeal circulation 8 and 24 hours after closed valvulotomy. The last case, in which the laceration was produced with a transventricular dilator, was saved by immediate open repair with pump oxygenator. While the oxygenator was being sterilized and donors cross matched, the patient's lungs were protected from serious congestion by tamponading the lacerated leaflet with the intracardiac finger. Perfusion was established 2 hours after the laceration, and the leaflet was carefully sutured through a long life atrial incision. Recovery was uneventful. These experiences have led to the following conclusions: mitral valve lacerations will occur occasionally with all technics of valvulotomy; the laceration, if serious, should be repaired immediately by an open method; the index finger should be left in the atrium to prevent regurgitation and pulmonary edema while extracorporeal circulation is being established.

Relationship Between Blood Concentration of Norepinephrine, Cardiac Output, and Resistance

Robert Eich, Richard Cuddy, Harold Smulyan, and Joseph Barry, Syracuse, N. Y.

Blood catechol amines and hemodynamics before and during *l*-norepinephrine (NE) infusion were measured in 26 subjects with labile hypertension. Cardiac outputs (COP) were done by the indicator-dilution technic, and blood catechol amines by the trihydroxyindol method. NE was infused at 7.5 μg./min. for 10 minutes, followed by either 11 or 14 μg./min. for another 10 minutes. During the eighth minute of each infusion rate, repeat measurements were made. In 20 patients, the study was repeated on the following day. The mean resting values were COP 7.32 L./min., pulse 79, BP 105 mm. Hg, total peripheral resistance (TPR) 1219 dynes/cm.$^{-5}$ seconds, and catechol amines, arterial NE .26, E .37, venous (antecubital) NE .30 and E .26 μg./L. Although there were some variations between subjects, following infusion of NE at 7.5 μg./min., the mean COP decreased .35 L./min., the rate 6.9, while the BP rose 9.88 mm. Hg, the TPR 196 dynes/cm.$^{-5}$ seconds, the arterial NE 1.28, and venous 1.05 μg./L. Increasing the infusion speed to 14 μg./min., while continuing to raise the blood pressure, lower the pulse, and increase the arterial and venous NE levels, increased the TPR only 54 dynes/cm.$^{-5}$ seconds because of a concomitant rise in COP of .23 L./min. There was no correlation between the catechol amine levels and the hemodynamic response, nor between infusion rate and blood level. Fourteen μg./min. given first produced a fall in COP of .60 L./min. and rise of TPR of 263 dynes/cm.$^{-5}$ seconds. These data suggest a limitation in the vasoconstrictor effect of infused norepinephrine, and fail to demonstrate any relationship between hemodynamics and blood catechol amines.

Isolated Aortic Stenosis in Adults: A Follow-up Study of 142 Patients Operated by the Closed Transaortic Technic

Laurence B. Ellis and Dwight E. Harken, Boston, Mass.

At the present time there are a number of approaches to surgery for calcific aortic stenosis. To evaluate these it is necessary to know the extent of preoperative disability and other characteristics of the patient population, the operative risk, and the long-term results.

In 142 consecutive transaortic operations, the operative mortality was 13 per cent in class 3 patients and 40 per cent in class 4. Seventy-seven class 3 patients have been followed 6 months to 5 years; 21 have died and the improvement rate of the survivors of operation has dropped from 76 per cent at 1 year to 50 per cent at 3 to 5 years. Seventeen class 4 patients have been followed 6 months or more; 8 have died, the percentage improved has fallen from 53 at 6 months to 20 at 2 to 5 years. The age and sex of the patients, preoperative symptomatology, heart size, associated aortic insufficiency, findings at surgery, and adequacy of the operations are discussed in relation to these clinical results.

The present study provides information to which the technics of transventricular valvuloplasty and open repair can be compared. The authors have had experience with these, as well as prosthetic

valve replacement which is the goal which may be the ultimate solution in selected patients with this disease.

Plasma Heparin Levels: Normal Values and Correlation with Serum Cholesterol and Low-density Lipoproteins

Hyman Engelberg, Beverly Hills, Calif.

The endogenous heparin(s) content of duplicate 5 ml. aliquots of plasma has been extracted and biologically assayed by its anticoagulant activity in 256 normal individuals. The range of values was from 10 to 24 units per cent (1.0 to 2.4 mg./100 ml. plasma). There was little variation in the average values from 10 to 80 years of age, and there was no difference between the sexes.

Serum cholesterol was measured in 260 individuals who had duplicate heparin determinations on plasma aliquots, and in addition, low-density lipoproteins were ultracentrifugally analyzed in 208. The correlation coefficient (r) was obtained for heparin versus cholesterol and heparin versus lipoproteins in both sexes below and over 50 years of age. There was no significant relationship between heparin levels and Standard S_f 0-12 lipoproteins in either sex. All correlation coefficients for heparin versus cholesterol and heparin versus Standard S_f 12-400 lipoproteins were negative, i.e., cholesterol and S_f 12-400 lipoproteins decreased as heparin increased. The correlation was statistically significant ($p < 0.01$) in all males, but in females was significant only for the lipoproteins. The coefficients were relatively low numerically. The results indicate that heparin is a regulator of serum lipids and that other factors are also influential.

Long-term Observations of Intermittent Heparin Therapy for the Prevention of Coronary Atherosclerosis

Hyman Engelberg and Robert Kuhn, Beverly Hills, Calif.

During the past 9 years, 66 private patients with previous myocardial infarction have received heparin therapy for a prolonged period. Concentrated aqueous heparin was given subcutaneously in doses of 200 mg. twice weekly, 3 times a week in a few instances. There were 3,912 months of therapy, or an average of 59.3 months per patient. During this time 10 patients died giving an over-all mortality of 15.2 per cent, a mortality rate of 3.1 per cent per year. There were no hemorrhagic deaths.

Although a strict control group was not followed during the entire period, it is our opinion that the mortality rate of 3.1 per cent indicates a 70 to 75 per cent reduction in anticipated mortality. This is based on an observed mortality rate of 11.5 per cent per year in a control group which was followed for 2 years. The low incidence of deaths in the heparin group is particularly significant since many of the patients had had several previous infarcts, had not responded to dietary measures by a lowering of their serum lipid levels, or had had recurrence of infarction while on oral anticoagulant therapy. These results demonstrate that intermittent heparin therapy is effective and feasible in the prophylaxis of coronary atherosclerotic disease.

Ventricular Septal Defect with Transposition of Aorta Masquerading as Acyanotic Ventricular Septal Defect

Mary Allen Engle, George R. Holswade, Wallace G. Campbell, and Henry P. Goldberg, New York, N. Y.

The unexpected finding of complete transposition of the aorta in the presence of normal position of the pulmonary artery was encountered in 2 patients undergoing open heart surgery for ventricular septal defect. This condition presents problems both in recognition and correction.

Under observation from ages 6 and 8 weeks, these acyanotic patients' symptoms, physical findings, and laboratory studies were characteristic of a large ventricular septal defect. Cardiac catheterization prior to surgery at ages 2½ and 3 years demonstrated pulmonary arterial hypertension in the range of systemic pressure, with a large left-to-right shunt at the ventricular level and no evidence of right-to-left shunting by oxygen analyses or dye-dilution studies. In the second patient, angiocardiograms showed aortic opacification at the normal time. In retrospect, the anterior position of the aorta could be recognized in the lateral view.

At operation, the aorta was considered to override a large defect in the anterior membranous septum, which was closed with sutures. At autopsy this defect extended into the inflow tract of the right ventricle where the aortic valve was transposed. The only outlet from the left ventricle was through the septal defect.

This experience suggests that angiocardiography should be performed in evaluation of patients with ventricular septal defect and a systemic pressure in the right ventricle. Forewarned, the surgeon might close the defect with a sling-like prosthesis that would leave the aorta in unobstructed continuity with the left ventricle. These studies in 3 other children are considered to confirm the diagnosis of this malformation.

Spectrum of Cardiac Anomalies Associated with "Corrected Transpositon" of the Great Vessels

Mary Allen Engle, Israel Steinberg, Daniel S. Lukas, and Henry P. Goldberg, New York, N. Y.

The position of the arterial trunks in "corrected transposition" is such that the aorta is anterior and lateral to the posteriorly and medially placed pulmonary artery. Commonly, the ventricular structures are reversed and mirrored. When venous return to the heart leaves through the appropriate vessel without obstruction or detour, the condition is completely "corrected."

Studies on 46 patients, with postmortem confirmation in 17, showed complete correction in only 1, a patient with atrioventricular dissociation. The imperfect correction in the others was due to the same anomalies, singly and in combination, as exist in patients with arterial trunks in the normal relationship. Four patients were classified as acyanotic, 15 potentially cyanotic, and 27 cyanotic. Fourteen had dextrorotation of the heart or dextrocardia; 1 had situs inversus with levocardia. Heart block was complete in 2 and incomplete in 8.

While the unusual position of the vessels and ventricles produced certain changes in physical examination, electrocardiograms, x-rays, cardiac catheterization, and especially in the angiocardiogram, the associated anomalies determined the clinical picture. For example, 14 "potentially cyanotic" patients had a ventricular septal defect, but when this was combined with severe pulmonic stenosis in 9, they were cyanotic and resembled the tetralogy of Fallot.

Angiocardiography is the most valuable technic for identification of the "corrected transposition" and demonstrates the variations in the sizes of these vessels and the intracardiac configuration when the arterial trunks in "corrected transposition" are associated with a variety of cardiac malformations, such as ventricular septal defect, single ventricle, left-sided Ebstein's anomaly of the tricuspid valve, infundibular pulmonic stenosis, and hypoplastic left heart with coarctation.

Evaluation of Direct-writing Phonocardiography as a Diagnostic and Clinical Teaching Device

Blair D. Erb,† John W. Evans, and Daniel A. Brody, Memphis, Tenn.

During the past year, we designed and constructed a direct-writing phonocardiograph which had an apparently adequate figure of merit (virtually uniform frequency response from 20 to 400 cycles per second). In a pilot study of 30 subjects, comparative phonocardiograms were recorded simultaneously by the direct writer and a conventional photographic unit. Although the latter produced more sharply inscribed tracings, the direct writer produced records of essentially identical form and clinical diagnostic content.

Directly inscribed phonocardiograms of 100 subjects with interesting and/or perplexing auscultatory findings were compared with the previously recorded results of careful stethoscopic examination. Of 133 murmurs which were both recorded and heard, phonocardiography corrected or modified clinical impressions regarding temporal relationships in 24, and envelope configuration in 9. Only 4 murmurs were recorded but not heard. Graphic registration proved of greatest value in the analysis of transient heart sounds, providing significant or clinically definitive additional information in 48 instances. As with conventional instruments, the registration of soft murmurs often proved difficult or unsatisfactory. However, a recently developed limiting circuit promises to minimize this failing considerably. In general, we find phonocardiography to be a highly effective diagnostic and clinical teaching procedure in difficult and puzzling auscultatory problems. The capability for continuously monitoring technical quality and specific diagnostic content of tracings by immediate inspection during the registration procedure makes the direct writer especially effective for such application.

Influence of the Peripheral Vascular Bed on the A-V Difference and Disappearance Curve of Injected Materials

Edward H. Estes, Jr., Samuel J. Friedberg, Robert F. Klein, and Morton Bogdonoff, Durham, N. C.

In a recent study of the limb A-V difference of labeled albumen-bound palmitic acid, the constantly positive A-V difference seen during an infusion of label was suddenly reversed during the decline of activity following cessation of the infusion. This was first interpreted as due to exit of label from the vascular compartment into a "fatty acid space," with re-entry into the vascular compartment after the infusion was stopped.

The phenomenon was studied further in 9 subjects. Albumen-bound palmitic acid-1-C^{14} was quickly injected into an antecubital vein and multiple simultaneous samples drawn from the brachial artery and an antecubital vein of the opposite arm. In 2 subjects, Evans blue dye was injected via the same syringe. Concentration curves of C^{14} showed a remarkable delay in rise in the venous concentration curve, with frequent reversal of the A-V difference on the descending limb. The initial contour of the curves was the same for Evans blue and C^{14}-palmitate.

The reversal of A-V difference can be explained by a long temporal delay in passage of blood through the arm rather than exit of label into an extravascular space. These observations agree with those of Freis, who reported a mean arm cir-

circulation time of 59 seconds. Venous tourniquets exaggerated the delay and also the reversal of A-V difference.

In consideration of A-V differences and curves of disappearance of rapidly fluctuating substances, failure to account for the effect of the peripheral vascular bed may result in serious errors in interpretation of data.

Comparative Proximity and Remoteness Characteristics of Conventional Electrocardiographic Leads: Relationship to the Electroposition Concept

John W. Evans, Blair D. Erb,† and Daniel A. Brody, Memphis, Tenn.

The Einthoven limb leads have historically been treated as remote leads, and the unipolar precordial leads as proximity leads. On the other hand, the direct relationship of the unipolar extremity leads to the Einthoven leads was initially emphasized; later, in accordance with Wilson's electroposition concept, proximity characteristics were ascribed to these leads.

In order to assess the relative remoteness or proximateness of various electrocardiographic connections, we mapped lead field isopotentials on the body surface of 7 human subjects. Maps of all 6 limb connections were plotted in 4 cases; Einthoven leads only—1 case; augmented unipolar leads only—2 cases. The following lead fields were mapped in the sagittal plane of a homogeneous torso model: midsternal-V (near V2), midvertebral-V (near VB), midsternal-F (near CF2), neck–lower extremities ("Y").

Lead characteristics were determined by lead field behavior as extrapolated to the cardiac region from the body surface maps. On this basis, the leads were graded as remote (lead field flowlines essentially rectilinear and parallel), semiremote, intermediate, semiproximate, and proximate (flowlines emanating in rectilinear pencils from a virtual point).

We find aV_L and the 3 chest leads to be proximate or semiproximate; lead I, intermediate; "Y", II, III, aV_R, and aV_F, remote or semiremote. Curvilinear lead field distortion was of significant degree in I and the midsternal-F lead, and essentially absent in the other leads. The relative remoteness of 2 of the 3 unipolar extremity leads is incompatible with the requirements of the electroposition concept.

Rebound Phenomenon in Acute Rheumatic Fever

Alvan R. Feinstein and Mario Spagnuolo, Irvington-on-Hudson, N. Y.

Clinical or laboratory abnormalities often reappear in acute rheumatic fever in the absence of a new streptococcal infection. This rebound phenomenon has been analyzed in 415 consecutive cases of children and adolescents with acute rheumatic fever.

Abnormalities only in CRP or sedimentation rate recurred in 112 patients, even in some who had been untreated, and invariably subsided spontaneously without clinical sequelae. Their treatment with suppressive agents was sometimes followed by a clinical rebound.

Clinical rebounds, manifested by fever and/or joint features and/or new cardiac signs, appeared shortly after cessation of therapy in 64 patients, but did not occur in untreated patients. They were more frequent in patients with more severe initial cardiac damage. Their incidence was higher after steroids alone (increasing with increasing length of treatment) than after salicylates alone (occurring only in patients treated for less than 8 weeks). Their incidence could be significantly reduced by combined therapy in which salicylates were continued after steroids were stopped.

Clinical rebounds brought new carditis to 13 of 46 patients with previous heart involvement, but brought severe cardiac features only to those who already had significant cardiomegaly; they did not create carditis where it did not exist previously. Untreated clinical rebounds in 31 patients usually subsided spontaneously within 2 weeks and left no specific residual effects. Retreatment of 33 patients was followed by subsequent clinical rebounds in 25.

These results indicate that many rebounds are preventable, that most of those which occur are best left untreated, and that their treatment may only prolong rheumatic activity without clinical benefits. The data contradict the current hypotheses that rebounds are due to spontaneous polycyclic rheumatic activity or to inadequate duration of therapy. They suggest that a rebound represents the "combustion" of the residual rheumatic inflammation which accumulated under the preceding therapeutic suppression.

Effect of Graded Doses of Norepinephrine on Forearm Blood Flow and on Arterial Pressure Before and After Chlorothiazide in Normal Subjects

Khalil A. Feisal, A. W. Horsley, and John W. Eckstein, Iowa City, Iowa*

Observations were made on 5 men before and during intravenous infusion of norepinephrine in doses of 0.075, 0.15 and 0.30 μg. of base per pound per minute. Forearm blood flow was measured plethysmographically and arterial pressure with a cuff. Measurements were repeated after 1 week of chlorothiazide administration (1.0 Gm. daily).

With the largest dose of norepinephrine, blood flow *decreased* by an average of 0.7 ml. per 100 ml. of forearm volume (15.6 per cent) before chlorothiazide and *increased* by an average of 1.2 ml. (42.3 per cent) after chlorothiazide ($p < 0.05$). Forearm vascular resistance (mean arterial pressure divided by blood flow) increased by an average of 15.2 units (66.7 per cent) before, and decreased by 1.2 units (0.7 per cent) after chlorothiazide ($p < 0.01$).

For the intermediate dose of norepinephrine, blood flow decreased by an average of 0.6 ml. (13.6 per cent) before, and increased 0.4 ml. (17.5 per cent) after chlorothiazide administration ($p < 0.05$). Resistance increased by an average of 8.6 units (37.5 per cent) before, and 0.6 units (5.6 per cent) after chlorothiazide.

The responses of blood flow and resistance following the smallest dose of norepinephrine and of mean blood pressure for all doses of norepinephrine were not altered significantly by chlorothiazide. Repetition of these studies 1 week after discontinuing chlorothiazide revealed responses similar to those observed before the drug. In these experiments chlorothiazide decreased the vascular responsiveness to norepinephrine.

Incrimination of the Capillary Bed in Acute Hypertension

Frank A. Finnerty, Jr., and John Merendino, Washington, D. C.*

The effect of acute reduction of arterial pressure on plasma volume, arterial hematocrit and red cell mass was studied in 24 hypertensive subjects. Nine were diagnosed acute (recent rise in arterial pressure and retinopathy) and 16 were chronic. Reduction in the mean arterial pressure (hexamethonium or guanethidine) in the 16 chronic patients from an average of 143 ± 21 to 98 ± 17 mm. Hg (34 per cent) was associated with an increase in plasma volume from average of 2.8 ± 0.4 to 2.8 ± 0.5 liters (3 per cent), a decrease in hematocrit from an average of 39 ± 5 to 37 ± 5 per cent, and a decrease in plasma protein from an average of 7.8 ± .45 to 7.4 ± .7 Gm./100 ml. A reduction in mean arterial pressure from an average of 177 ± 20 to 124 ± 15 mm. Hg (30 per cent) in the 9 patients with acute hypertension was associated with an increase in plasma volume from an average of 2.6 ± 0.5 to 2.9 ± 0.5 liters (12 per cent), a decrease in arterial hematocrit from an average of 40 ± 7 to 38 ± 7 per cent, and a decrease in plasma protein from an average of 7.7 ± .84 to 7.3 ± .78 Gm./100 ml. No change in the red cell mass occurred. The changes in cardiac output were not significantly different in either group.

It is postulated that the greater hemodilution which followed the reduction in arterial pressure in the acute patients was due to a generalized (venous + arteriolar) rather than a local (arteriolar) reduction in peripheral resistance which disturbed capillary filtration pressure and thus permitted a shift of fluid across capillary membranes.

The lack of significant change in total protein concentration in the acute group and a *decrease* in plasma volume from an average of 3.1 ± 0.4 to 2.6 ± 0.9 liters (15 per cent) in 10 normotensive subjects during norepinephrine infusion supports this interpretation of the data.

Ophthalmoscopic Picture in Hypertensive Patients with Chronic Glomerulonephritis

Frank A. Finnerty, Jr., Alvin Parrish, Gloria DeCarlo Massaro, and Leonard Berman, Washington, D. C.*

Recent experience has suggested that ophthalmoscopic examination may be useful in detecting chronic glomerulonephritis in the nonpregnant hypertensive patient just as it has been useful in diagnosing toxemia in the hypertensive pregnant patient. Retinal edema and generalized spasm of the retinal arteries are prominent features in both diseases. In addition the absence of arteriosclerosis (arteriovenous nicking) is striking despite a long history of hypertension. The validity of these preliminary observations was tested by serial retinal photography in 17 hypertensive subjects with proven glomerulonephritis. Retinal edema (which either disappeared or diminished following diuretic therapy) and generalized arterial spasm were present in 14 patients. Despite a history of hypertension in each patient for more than 8 years, arteriovenous nicking was present in only 3 patients.

Renal biopsy was performed in 9 additional subjects with hypertension of unknown etiology who manifested retinal arterial spasm, retinal edema and/or absence of arteriosclerosis. Subacute or chronic glomerulonephritis was the histologic diagnosis in each. Repeated urinalyses failed to reveal albumin, red blood cells or casts in 6 patients.

These findings suggested: (1) that the combination of retinal edema, retinal arterial spasm and absence of arteriosclerosis frequently characterizes the ophthalmoscopic picture of hypertensive patients with chronic glomerulonephritis; (2) that the ophthalmoscopic findings may be useful in pointing to the etiology of hypertension; and (3) if these findings are borne out by further studies it will be necessary to change our concept of the frequency of glomerular disease in the etiology of hypertension.

Supernormal Phase of A-V Conduction Due to Potassium

Charles Fisch, Indianapolis, Ind.

Supernormal phase of A-V conduction manifested by alternating A-V conduction has been observed in man, but it is doubtful if this phenomenon has ever been experimentally produced in an intact mammal. Although A-V blocks are a rather frequent manifestation of hyperkalemia, supernormality of A-V conduction due to potassium has never been described.

In the course of the last 73 infusions of K to 15 dogs, supernormal phase of A-V conduction was observed on the oscilloscope and recorded 43 times. The phenomenon was manifested by alternation of A-V conduction time with "paradoxical" shortening of P-R when the latter followed a short R-P, and prolongation of P-R when the preceding R-P became longer. The difference between the alternating R-R varied in different experiments. For example, in animal 35, experiment 96, the shorter R-R measured 0.28 seconds and the longer 0.40 seconds. Not infrequently the difference between the alternating R-R intervals would become progressively greater due to gradual prolongation of P-R, and second degree heart block, with or without Wenchebach phenomenon, would appear. On occasions the second degree block would suddenly give way to 1:1 response with recurrence of supernormality of conduction.

The effects of vagus, changes in length of refractory period due to variation of R-R, concealed conduction, premature and escape beats as cause for alternation of A-V conduction were excluded.

Use of a Sharp Stylet for Interatrial Septal Passage of the Radiopaque Right Heart Catheter into the Left Heart

Don L. Fisher, George R. Logsdon, and Maurice H. McCaffrey, Pittsburgh, Pa.

A sharp stylet has been used in 25 patients to permit catheter penetration of the interatrial septum for left heart catheterization. A tapered, curved PE-205 (8F) radiopaque polyethylene catheter is first inserted into an arm vein or saphenous vein. It is then positioned fluoroscopically at the right atrial septal area of the fossa ovalis. The stylet is inserted, consisting of a specially shaped 18 or 19-gage thin-walled needle with blunt obturator. The catheter and sharp stylet are advanced together, piercing the septum in a left-posterior direction so as to avoid the aorta. The catheter alone is manipulated further, entering the left ventricle. It is thereafter withdrawn through the atrial septum for right heart catheterization. No shunts through the site of perforation can be found, nor have other complications been attributed to the septal perforation. The method is probably safer and more convenient than some other left heart catheterization procedures, especially in patients with small left atria.

The procedure differs from the transseptal methods of Ross and of Cope in 2 important ways. First, arm veins may be used, as well as the saphenous vein. Secondly, a large radiopaque catheter is advanced to the left heart rather than a small radiolucent plastic tubing. This allows superior pressure recordings and cardioangiographic injections. A direct test for aortic regurgitation has been applied, with injection of blue dye above the aortic valve (using an additional retrograde arterial catheter) and aspiration of regurgitated tracer material through the left ventricular catheter.

Congenital Heart Disease in the Fifth to Eighth Decades of Life

June M. Fisher, William R. Wilson, and Ernest O. Theilen, Iowa City, Iowa

Information concerning the natural history of congenital heart disease will be increasingly difficult to obtain because of aggressive surgical treatment. Congenital lesions are frequently unrecognized or misdiagnosed in middle and old age. Thirty-seven patients, 43 to 78 years of age, with various congenital heart defects were seen in the Cardiovascular Laboratory over the past 9 years (an incidence of 3.5 per cent of total catheterizations). Before catheterization, 15 had been misdiagnosed as rheumatic, arteriosclerotic, or pulmonary heart disease.

Atrial septal defects were the most common lesions, occurring in 19 patients. All but 1 were symptomatic (functional class II or III). In several, the symptoms were recent in onset but rapidly progressive. Fourteen had systolic pulmonary artery pressures greater than 40 mm. Hg. Six patients had closure of their defects and became asymptomatic.

Patent ductus arteriosus was found in 9 patients; 5 were asymptomatic. Pulmonary hypertension (from 50 to 116 mm. Hg, systolic) was present in 4. Surgical treatment was contraindicated in 2 cases because of pulmonary hypertension or extensive calcification in the ductus.

In general, isolated pulmonic stenosis was well tolerated in our 6 patients despite significant gradients between the pulmonary artery and right ventricle. A 70-year-old patient with cardiac failure had coexistent coronary artery disease. One patient with pure infundibular stenosis had an infundibulectomy; his postoperative catheterization was normal.

Ventricular septal defects were uncommon. Two of the 3 patients in whom the diagnosis was made were asymptomatic with normal pulmonary artery pressures. No patients with tetralogies or trilogies were seen.

Observations on Left Ventricular Pressure and Ejection Dynamics in Hypothermia

Walter L. Floyd, Marcus L. Dillon, Durham, N. C., and Arnold M. Weissler, Galveston, Texas

By means of a rapid-response electromagnetic flowmeter which allowed accurate determination of quantity, time, and character of left ventricular ejection, and simultaneous measurement of intraventricular, central aortic, and left atrial pressures, left ventricular dynamics were measured in thoracotomized, anesthetized dogs in the normothermic and hypothermic states. Heart temperatures of 22 C. to 25 C. were induced by cooling the venous blood, using a heat exchanger and extracorporeal circuit. Observations were made at a relatively constant filling pressure (2 to 3 mm. Hg).

In a representative experiment, heart rate and cardiac output fell to 33 per cent of control values, while stroke volume remained constant. Time of isometric contraction was unchanged. Duration of systole became double its control value (.13 to .26 second), but duration of forward flow was not increased proportionally, which demonstrated that a large portion of systole was spent without measurable ejection of blood occurring. Isometric relaxation was prolonged 12-fold (.01 to .12 second). The period of rapid ventricular filling was replaced by a gradual and equal fall in atrial and ventricular pressures, indicating that rapid filling is obliterated or impaired by gradual relaxation extending far into diastole.

The following conclusions were drawn from these observations: (1) the events of the cardiac cycle are not altered to the same degree by hypothermia; (2) ejection of blood from the cold heart is accomplished in a relatively inefficient manner; (3) the abnormal myocardial tone of the hypothermic heart impairs the ability of the ventricle to relax and allow efficient, rapid ventricular filling.

Renal Extraction of Serum Nonesterified Fatty Acids

Allan L. Forbes and Joseph H. Magee, Richmond, Va.

Serum nonesterified fatty acids (NEFA) were determined by the method of Dole, with excellent reproducibility of replicates, in arterial and renal venous blood samples drawn simultaneously prior to renal clearance studies in 5 hypertensive and 2 normotensive subjects. Samples were drawn after an overnight fast and following ingestion of 1,500 ml. of water to initiate water diuresis. Saline without heparin was used to maintain patency of the venous catheter. Position of the catheter was ascertained by fluoroscopy and oximetry, and verified, subsequent to sodium p-aminohippurate (PAH) administration, by extraction of PAH. In 6 instances of right renal venous catheterization, the mean NEFA extraction was 20.7 per cent with a mean arterial level of 0.970 mEq./L. In 3 instances of left renal venous catheterization, extraction was much less (4.5 per cent, with a mean arterial level of 1.140 mEq./L.), probably due to mixing of renal venous blood with venous blood from other sources.

Preliminary studies suggest the possibility that NEFA uptake by the kidney is in part related to renal synthesis of triglyceride, as judged by renal venous plasma determinations. Our studies to date do not permit evaluation of NEFA as a renal energy source, nor the role of renal lymph in NEFA uptake.

Permeation of Anionic Metabolites into Muscle

Ernest C. Foulkes and C. M. Paine, Cincinnati, Ohio*

Myocardium and other tissue readily utilize anionic metabolites such as lactate and the lower fatty acids. In rat diaphragm, the uptake of these metabolites is mediated by a temperature and concentration dependent system in the cell membrane. All acids found to possess affinity for the transfer mechanism are lipid-soluble monocarboxylic acids. These results were obtained in studies on the ability of low concentrations of many anions to depress competitively the uptake of acetate. This uptake was not affected by compounds in which a sulfonic acid residue was substituted for the carboxy group, or in which a hydroxy group was introduced, as in glycolate ($CH_2OH.COO^-$). Propionate competes readily with acetate; measurable activity is still observed with L-lactate, but the dihydroxy compound (glycerate) is without effect. That lipid solubility helps determine affinity for the transfer system is further suggested by the observation that other polar groups (NH_2,COOH) also abolish activity: all dicarboxylic and amino acids tested proved inert. The influence of steric factors is indicated by the inability of benzoate to compete with acetate. The uptake system is inhibited by protamine and by compounds of Hg; there is no effect of hydrocortisone or insulin. The presence in the cell membrane of such a facilitated diffusion mechanism may account for the ready diffusibility of certain anionic metabolites in vivo.

Idiopathic Cardiomyopathy

Noble O. Fowler, Mosche Gueron, and David T. Rowlands, Jr., Cincinnati, Ohio

This study describes 18 patients who died of congestive heart failure without clinical or pathologic evidence of a primary cause. Their ages were from 18 months to 68 years at death. Seven patients had heart failure for 5 years or more; 3 had heart failure for over 10 years. Seven patients were alcoholic and 3 had nutritional cirrhosis. Transient mitral or tricuspid systolic murmurs and apical protodiastolic gallop rhythm were common. Atrial fibrillation was present in 6 patients. The electrocardiograms revealed abnormal left-axis deviation in 5 and left bundle-branch block in 2.

Right heart catheterization in 4 patients showed low cardiac output, increased arteriovenous oxygen difference, and elevation of pulmonary arterial, pulmonary wedge, right ventricular diastolic, and right atrial pressures.

Heart weights exceeded 500 Gm. in 13 patients. All 18 had left ventricular hypertrophy. Mural thrombi were present in 11; 4 had pulmonary emboli and 4 had systemic arterial emboli. No patient had gross myocardial scarring or evidence of myocarditis. Ten had focal increases of elastic tissue.

Idiopathic cardiomyopathy may simulate coronary artery disease because of the abnormal electrocardiogram, hypertensive heart disease because of elevation of diastolic blood pressure during heart failure in some patients, or pericardial effusion because of poor cardiac pulsations, narrow pulse pressure, and paradoxical pulse. It may mimic rheumatic heart disease because of systolic murmurs, left atrial enlargement, and Kerley lines. The cause is unknown. Only 1 patient had a familial history of similar heart disease.

Left Ventricular Ejection Velocity and Acceleration Studies in Intact Man

Samuel M. Fox, III, G. Octo Barnett, Alexander J. Mallos, Donald L. Fry, and Joseph C. Greenfield, Jr., Bethesda, Md.

In 27 patients, a double-lumen catheter provided a continuous approximation of the instantaneous ascending aortic blood velocity by the computed pressure gradient technic. Peak velocities were usually achieved early in the ejection period. The ratio of the time to achieve peak velocity to the total ejection time was increased in those subjects with diseased hearts. The peak ejection velocities at rest of 2 males who were found to have no demonstrable heart disease were just under 100 cm./sec. The maximal acceleration in these subjects exceeded 2,500 cm./sec.^{2}, while the mean acceleration from initiation of ejection to peak was over 900 cm./sec.^{2}.

Patients with various forms of cardiac insufficiency tend to have significantly reduced acceleration with a velocity-time contour becoming less rectangular and more that of an isosceles triangle.

A patient recovering from myocarditis was studied before and after marked clinical improvement. There was a more striking change in resting acceleration and velocity than improvement in either resting or exercise cardiac output or mean stroke volume.

The increase in velocity after cessation of 2 minutes of 10 pounds weight lifting was usually greater than the changes during the exertion itself compared to the resting control. The Valsalva maneuver proved useful in demonstrating the ability of the left heart to augment output during the "overshoot" in phase IV.

These studies lend support to the hypothesis that velocity and acceleration determinations give a sensitive indication of the functional status of the myocardium.

Role of Carotid and Intracardiac Baroreceptors and of Vasoactive Drugs in Control of the Venous Bed

Charles J. Frahm, John Ross, Jr., and Eugene Braunwald, Bethesda, Md.

The effects of stimulation of carotid and intracardiac baroreceptors on the capacity of the total systemic vascular bed, on venous distensibility and venous return were studied in an experimental preparation in which the use of extracorporeal circulation permitted complete hemodynamic isolation of the carotid sinuses and of the heart and lungs. Alterations of intravascular blood volume and venous return were measured continuously. Brief occlusion of the venous outflow line permitted inscription of venous pressure-volume curves. Elevation of perfusion pressure in the isolated carotid sinuses (4 dogs) produced venodilatation and an augmentation of intravascular blood volume, averaging 12.9 ml./Kg.; when carotid sinus pressure was decreased, venoconstriction occurred, intravascular blood volume diminished and venous return to the oxygenator increased by 27 per cent of the control level. Elevation of intracardiac pressures (8 dogs) produced venodilation with an increase of intravascular blood volume, averaging 6.9 ml./Kg., and a decrease in venous return, averaging 25 per cent of control perfusion rates. Infusion of norepinephrine (7 dogs) resulted in venoconstriction with a decline in intravascular volume averaging 19.0 ml./Kg., and an increase in venous return, averaging 40

per cent of the control level. Arfonad infusion (4 dogs) resulted in venodilatation, an augmentation of blood volume averaging 17.3 ml./Kg., and a decrease in venous return averaging 30 per cent of the control. Alterations in venous distensibility were consistent with the observed changes in vascular capacity. These experiments indicate that the distensibility of the total venous bed, the total intravascular capacity, and venous return are controlled reflexly by baroreceptors in the carotid sinuses and heart and are modified directly by vasoactive drugs.

Estimated End-diastolic and Residual Right Ventricular Volumes in Man Using Indocyanine Green

Edward D. Freis, George L. Rivara, Anthony N. Damato, and Bruce L. Gilmore, Washington, D. C.

Right ventricular volume was estimated using a Rodriguez injection catheter in the right ventricle and 100 cm. Goodale-Lubin collection catheter in the proximal pulmonary artery. Sampling catheter blood was pulled through a modified recording densitometer at high velocities ($> 1 \times$ vol. catheter/sec.) to permit adequate rendition of the step-like washout curve. Cardiac output and mean stroke volume were determined by brachial arterial sampling during passage of the same bolus of dye. Per cent residual volume was estimated from the ratio of dye concentrations of the fourth (Cm^4) to the third (Cm^3) beats following injection when mixing appeared to be essentially complete. Predicted and actual values for the number of beats required for 95 per cent dye disappearance at the percentage residual volume calculated as above generally were in good agreement. End-diastolic volume was estimated from the relation

$$EDV = \text{stroke volume}/1-\frac{Cm^4}{Cm^3} .$$

In 6 patients without cardiac disease and with normal right heart pressures and cardiac size by roentgenography, the end-diastolic volume averaged 147 ± 31 ml., of which the estimated residual volumes averaged 48 ± 5 per cent. Breath holding in 2 of these subjects decreased estimated residual volume to 24 and 25 per cent.

Application of an Intravascular Electrode for the Recording of Indicator-dilution Curves

Peter L. Frommer, William W. Pfaff, Eugene Braunwald, and Andrew G. Morrow, Bethesda, Md.

The polarographic technic described by Clark for recording of indicator-dilution curves has been applied to a group of dogs with experimentally produced left-to-right shunts, as well as to 50 patients with a variety of cardiovascular lesions. The sensing device, a platinum electrode, is introduced directly into a peripheral artery through an indwelling needle, or mounted at the tip of a cardiac catheter and introduced directly into the heart or great vessels. Ascorbic acid, a powerful reducing agent, was utilized as an indicator; the electrochemical behavior of this substance when in the immediate environment of the sensing electrode produces an increase in electric current that is proportional to its concentration. This current is amplified and recorded continuously, providing a time-concentration curve. The contour of ascorbic acid dilution curves is identical to that of simultaneously recorded dye-dilution curves. The Clark polarographic technic has the advantage of permitting the inscription of multiple dilution curves from a systemic artery or from the heart without requiring the sampling of blood. By placing the sensing device into the blood stream, it makes possible the recording of dilution curves without the distortion inherent in conventional blood sampling technics. The value of the intravascular electrode in the characterization of circulatory shunts and of valvular regurgitation has been demonstrated in a series of clinical examples.

Congenital Aplasia or Marked Hypoplasia of the Myocardium of the Right Ventricle (Uhl's Anomaly)

Benjamin M. Gasul, Bessie L. Lendrum, and Rene A. Arcilla, Chicago, Ill.

This anomaly has been described only once (1952). We wish to present the clinical and heretofore unreported angiocardiographic and hemodynamic findings on 2 infants. Both patients had cardiac decompensation in infancy, and case 1 died in severe congestive heart failure at 1 year of age. Case 2, now 11 months of age, has so far responded well to medical management. Both had congestive heart failure with diastolic gallop rhythm and feeble heart sounds, and marked cardiomegaly without evidences of pulmonary hypertension, right ventricular hypertrophy or tricuspid regurgitation. The chest roentgenograms showed marked cardiomegaly and normal and diminished pulmonary vascular markings. The electrocardiogram showed right atrial hypertrophy, left ventricular hypertrophy and, in case 1, small qR complexes in the right precordium which probably represented rsR′ pattern. Cardiac catheterization demonstrated normal systolic pressures in the lesser circulation, but markedly elevated end-diastolic waves in the right ventricle and pulmonary artery, which in case 1 had identical magnitude and temporal relationship with the right atrial *a* waves. We have not encountered, nor have we seen any reports in the literature of similar curves.

These catheterization findings indicate that the right ventricle functions mostly as a reservoir for the venous blood. The angiocardiograms revealed dilated right atrium and right ventricle, prolonged pulmonary circulation time, normally located tricuspid ring, and unusually thin right ventricular wall without any identifiable trabeculae. We believe that the diagnosis can be made from the clinical, catheterization, and angiocardiographic findings.

Geographic Patterns of Coronary Heart Disease Mortality in New York State

Frances R. Gearing and Morton D. Schweitzer, New York, N. Y.

Analysis was made of deaths attributed to arteriosclerotic heart disease in the 57 counties of New York State (exclusive of New York City) for the years 1949 to 1951. There was more than a twofold variation in the death rates per 100,000 population among these upstate counties. Relative death rates for the 2 sexes varied considerably from one county to another. Within a county the death rate was not consistently in the same quartile in successive decades of life.

Among women under 65, the age of occurrence of a specified death rate was 10 years later than among men. With increasing age, the interval decreased so that, after the age of 75, it was only 3½ years. There was little variation in the death rate among urban areas, although the urban areas had consistently higher death rates than the rural areas. Age-adjusted male death rates varied considerably more among rural areas than among the urban areas. There was no association between income and death rates, nor was any association found between high death rates and high production of dairy products or other crops.

Further epidemiologic studies of the populations in counties with high death rates and those with low death rates may provide clues concerning etiologic factors responsible for this disease.

Relationship Between Arterial Pressure and Exertional Angina Pectoris in Hypertensive Patients

A. J. Georgopoulos, F. M. Sones, Jr., and I. H. Page, Cleveland, Ohio

Elevation of arterial pressure (BP) has been observed during spontaneous attacks of angina pectoris (AP). Further, AP has been described in patients whose BP has been lowered. These observations suggest a possible etiologic association between the level of BP and AP, but this association has not been adequately studied.

This report describes the relationships among exercise, BP, and AP in 7 hypertensive patients with left ventricular hypertrophy and exertional AP. Coronary angiograms were performed in all. Five had segmental coronary arterial disease and 2 had normal vessels with predominant right coronary arteries.

Two-minute exercises were performed in sitting and supine positions. BP was measured sphygmomanometrically and electrocardiograms were taken serially. In the 5 patients with coronary disease, exercise in both positions caused striking BP elevation followed by AP and electrocardiographic changes (S-T segment depression with T-wave inversion). When the pressor response to exercise was eliminated by intravenous sodium nitroprusside, AP was prevented and electrocardiographic changes did not occur.

The 2 patients with normal coronary arteries had orthostatic and exertional hypotension secondary to antihypertensive drug treatment. In both, sitting exercise caused intense hypotension followed by AP and electrocardiographic changes. BP did not change during exercise in supine position; AP and electrocardiographic changes did not occur.

These results show that in hypertensive patients with coronary arterial disease, further elevation of BP during exercise is a causal factor in precipitating AP. In hypertensive patients with normal coronary arteries, exertional AP is precipitated only by hypotension.

Complete Correction of Tetralogy of Fallot: Analysis of Factors Contributing to Reduction in Mortality

Frank Gerbode, J. Bruce Johnston, George A. Harkins, Albert A. Sader, William J. Kerth, and John J. Osborn, San Francisco, Calif.

Open heart surgery has led to an improved understanding of the anatomy and physiology of the tetralogy of Fallot. At the same time, continuing experience with surgical repair, perfusion technics, and postoperative care has resulted in alterations in treatment yielding steadily improving results. Because alterations in technic and results of surgery strongly affect concepts regarding indications for surgery, selection of patients, and optimal age at which surgery should be recommended, we have attempted to demonstrate the dynamic changes which are taking place in the treatment of tetralogy of Fallot through an analysis of our total patient experience in the open correction of this condition.

Detailed discussion is given to the following:

1. Prognostic significance of the degree of outflow tract narrowing.
2. Benefits of profound hypothermia as an adjunct to cardiopulmonary bypass.
3. Use of drugs during and following perfusion.

4. Incidence of hematologic abnormalities.
5. Postoperative heart failure.
6. Indications for surgery at the present time.
7. Management of patients who are not candidates for complete correction.

The analysis includes more than 60 patients, and the acyanotic and cyanotic forms of tetralogy are discussed separately.

Endocardial Cushion Defects: Diagnosis and Technic of Surgical Repair

Frank Gerbode, J. Bruce Johnston, Saul Robinson, George A. Harkins, and John J. Osborn, San Francisco, Calif.

The development of cardiopulmonary bypass has led to a significant improvement in the understanding and treatment of the complex group of anomalies associated with abrupted development of the endocardial cushions. We have reviewed our experience with 15 patients with such defects and present an analysis of clinical findings, emphasizing the accuracy of the electrocardiogram in diagnosis.

The evolution of surgical technic has led us to stress the importance of 2 aspects of the operation. First, a step-wise inspection and repair of the 4 possible defects should be undertaken in the following logical sequence: mitral valve, atrial septal defect, ventricular septal defect, and tricuspid valve. Since following this order, we have encountered no defects that could not be repaired, nor have we had any residual defects. The second point in surgical approach has been the utilization of the insertion of the septal leaflet of the tricuspid ring as the base of the atrial septal repair. Since making this adjustment, we find we have no incidence of permanent heart block and no mortality in a series of 7 consecutive patients.

Features of postoperative management and follow-up on selective cases are included.

Citric Acid Metabolism in Cardiac Mitochondria

Menard M. Gertler, New York, N. Y.

Cardiac muscle, in contradistinction to skeletal muscle, derives the bulk of its energy from aerobic metabolism. Studies on the intermediates of the citric acid cycle, i.e., α-ketoglutarate, succinate, malate and fumarate revealed that the theoretic amounts of adenosine triphosphate (ATP) were derived from the oxidation of the various intermediates by guinea pig cardiac mitochondrial preparations. It has hitherto been thought that citric acid, a key metabolite in the citric acid cycle, is not oxidized by cardiac muscle. It has been found in this laboratory that citric acid will be oxidized by cardiac mitochondrial preparations, but there are 3 interesting phenomena associated with this oxidation: (1) a lag period of 10 minutes prior to the onset of oxidation, which then proceeds in a linear fashion; (2) the oxidation proceeds slowly and linearly with a QO_2^N of 260 as compared to a QO_2^N of 1,000 for α-ketoglutarate; (3) thirdly, but most important, there is absolutely no energy made available (no P/O ratio) from this oxidation in the form of bound ATP, whereas there are 4 moles of ATP made available from the oxidation of 1 mole of α-ketoglutarate. The rate of oxidation of citric acid may be enhanced by removal of hexokinase-glucose from the system or the addition of diphosphopyridine nucleotide (DPN) and triphosphopyridine nucleotide (TPN). The lag period does disappear with these changes in experimental procedure but, in spite of these changes in oxidative rates, phosphorylation does not accompany the oxidation.

Effect of *l*-Norepinephrine and Phenylephrine on the Rate of Posthemorrhagic Hemodilution

Stanley Giannelli, Jr., New York, N. Y., J. Robert Navarre, Toledo, Ohio, D. Raj Mahajan, and Gerald H. Pratt, New York, N. Y.

Splenectomized dogs were bled, upon a scale, of 3 per cent of body weight, within 2 minutes. Hemodilution was followed by serial venous hematocrits, a valid method since venous/body hematocrit ratio does not change in splenectomized dogs after massive hemorrhage or epinephrine administration. Arterial, venous, and portal pressures were monitored. Seven animals served for control hemorrhage. Seven animals received an infusion of .002 per cent *l*-norepinephrine in 5 per cent dextrose in water, started just when bleeding was completed; 8 animals received .01 per cent phenylephrine at rates that maintained the arterial pressure in the prehemorrhage range. Systemic and portal venous pressures also rose to previous levels. The maximum fluid administered, above urinary and insensible losses, was 2 ml./Kg. There was no significant difference in the average rate of hemodilution between the 3 groups. Hemodilution was completed within 20 to 30 minutes, when blood volume was about 120 per cent of the immediate posthemorrhage value. Because of the differences in arterial and venous pressures between the control group and the animals receiving the vasopressor agents, with, however, similar rates of hemodilution, it is postulated that posthemorrhagic hemodilution occurs in regions of the microcirculation that are isolated from the large artery and vein pressures by pressor amine-induced sphincteric action. In these areas of relatively low hydrostatic pressure, colloid osmotic

pressure would be more effective in drawing fluid into the vascular space.

Cor Triatriatum: Clinical, Hemodynamic and Autopsy Studies and Long-term Observations after Open Surgical Correction

James E. Gibbons, Wanda Jegier, and David L. Murphy, Montreal, Quebec, Canada

Experience with 3 patients illustrates the urgent need for early recognition of this congenital obstructing band in the left atrium.

The first patient, a 4-month-old male, died suddenly before cardiac studies were completed. A 3-year-old girl was under observation for 4 months prior to death. After hemodynamic and angiocardiographic studies, a presumptive diagnosis of primary pulmonary hypertension was entertained. An unexpected finding in the lungs at autopsy was extensive acute intimal necrotizing arteriolitis.

The third patient was a 16-month-old male who had increasing dyspnea and fatigue for only 3 weeks prior to referral. Digitalization did not alter the congestive failure status. Hemodynamic studies revealed marked elevation of pulmonary capillary pressure, pulmonary hypertension exceeding systemic levels, and a low cardiac output. The pulmonary hypertension was significantly reduced by inhalation of 100 per cent oxygen and intravenous acetylcholine. Unusual clinical features included a continuous murmur in the left axilla, and striking enlargement of the left atrium on x-ray. Complete excision of the obstructing membrane was accomplished at open operation with cardiopulmonary bypass. The striking clinical improvement has now been maintained for over 1 year; the right ventricular overload on the electrocardiogram has progressively returned to normal and normal hemodynamics were found at heart catheterization 6 months after surgery.

Effect of Thiazide Diuretics on Plasma Volume, Body Electrolytes, and Excretion of Aldosterone of Hypertensive Patients

Ray W. Gifford, Jr., Vernon R. Mattox, Alan L. Orvis, Don R. Mathieson, and Harold L. Mason, Rochester, Minn.

During the first week of treatment with a thiazide diuretic, the plasma volume, determined by dilution of Congo red dye for 19 of 21 nonedematous hypertensive patients, was reduced; the mean reduction was 8.8 per cent. Correlation between reduction in plasma volume and mean blood pressure seemed fairly good during the first week of therapy. Thereafter none existed, for although the blood pressure remained lower, the plasma volume tended to return to control levels in spite of continuing therapy. Forty-one determinations of plasma volume were made on 19 patients 12 days to 9 months after treatment with a thiazide diuretic was started. The mean change in plasma volume was a reduction of 2.6 per cent.

Eleven determinations of 24-hour exchangeable sodium and potassium, using radioactive isotopes, made on 5 nonedematous, hypertensive patients 5 days to 9 months after treatment with a thiazide diuretic was started showed no significant change.

The 24-hour urinary excretion of aldosterone was measured 16 times for 9 hypertensive patients at intervals of 3 days to 2 months after starting therapy with a thiazide diuretic. Except for a temporary elevation in 1 patient, values for aldosterone remained within normal range and were not significantly different from those before treatment.

These data indicate that the chronic hypotensive action of thiazide diuretics is not due to detectable depletion of plasma volume or body sodium. Therapy with thiazide diuretics did not induce an enduring state of secondary hyperaldosteronism in the nonedematous hypertensive patients studied.

Circulatory Bypass of the Right Side of the Heart. VI. Superior Vena Cava–Right Pulmonary Artery Anastomosis: Experimental Background and Clinical Application

William W. L. Glenn, Nelson K. Ordway, Remedios Sunico, Ruth Whittemore, and Marie J. Browne, New Haven, Conn.

Certain congenital cardiac anomalies characterized by malfunction of the right atrium or right ventricle, or both, that cannot be corrected by open heart surgery will benefit from an anastomosis of the superior vena cava, ligated at the atrium, to the distal end of the pulmonary artery.

On the basis of experiments, this procedure has been applied thus far to 6 patients with congenital malformations of the heart. Two had functional single ventricles and pulmonary stenosis with a transposed aorta and pulmonary artery; 2, both infants, had tricuspid atresia; 2 had tetralogy of Fallot with unusual complications—1, aged 41, had congenital complete heart block, and the other had multiple constrictions of the pulmonary artery. All patients have apparently been benefited as judged by the clinical course and arterial oxygen studies. Calculations based on arterial oxygen content show the postoperative right pulmonary flow at rest to be about 30 per cent of the total systemic venous return. This increased pulmonary flow—representing solely systemic venous and not mixed systemic venous and oxygenated blood as in extracardiac arterial shunts—has been accom-

plished without increase in the work of the heart. Details of the indications for this procedure, the technic of the operation and the postoperative care have also been studied.

Calcific Aortic Stenosis and Its Surgery—Open or Closed?

Robert P. Glover, Philadelphia, Pa.

Calcific aortic stenosis and its natural myocardial sequelae have remained more resistant to proper solution than any of the other stenotic valve problems. Valvular destruction and distortion in these lesions is so extreme that this structure can no longer be called a valve. The only obvious solution holding any prospect of long-term improvement is total resection and total replacement with a *suitable* prosthetic valve. Many precursors of such a valve have been used with occasional success, but for the most part the results have been poor. In the meantime, many such patients are doomed to an early demise, often with improperly attempted experimental surgery.

Although the ultimate goal is not being entirely served, there is available reasonable, palliative surgery often followed by amazingly good clinical improvement obtained with but a relatively low operative risk.

One hundred patients with calcific aortic stenosis operated upon by transventricular split-dilatation over the past 6 years are presented. In those treated before left ventricular failure developed the operative mortality was 6 per cent. Surgical intervention after the onset of myocardial failure resulted in a mortality of 15 per cent. Seventy-five per cent of these patients are alive and improved after 1 to 5 years and most of these have returned to full-time employment. These results are detailed and a classification for proper referral for surgery is stressed. Surgery in patients of this type is palliative but rewarding just as it is in many other forms of a malignant disease process.

Objective Evaluation of Myocardial Blood Supply In Vivo Through Observation of Acute Changes in Myocardial Temperature

Edward I. Goldsmith, New York, N. Y.

These experiments were designed to estimate the hemic perfusion of small peripheral masses of myocardium in living animals. A microprobe resistance thermometer small enough to embed in the myocardium without significant trauma and sensitive enough to detect small temperature changes (0.02 C.) rapidly (0.035 second) was used. Slight and transient temperature declines were recorded immediately after the blood had been "labeled" by the rapid injection of iced saline into the aortic root.

In normal animals, individually characteristic curves were observed in the right and left ventricular myocardium. On the left, the temperature decline was abrupt, rapid and deep. On the right, it occurred later and was less pronounced. In animals with myocardial infarction following gradual coronary occlusion, consistent deviations from the normal patterns were observed. In infarcted tissue, temperature declines were slight or absent. In adjacent, grossly normal areas, the response was more pronounced than normal. These changes correlated with the state of vascularity as interpreted by coronary arteriography and by microscopy.

These observations suggest the possibility of developing a quantitative method for measuring myocardial perfusion.

Role of Selective Retrograde Aortography in Congenital Heart Disease: Evaluation of "Lesions of Aortic Integrity"

Edward I. Goldsmith, Nathaniel Finby, and Mary Allen Engle, New York, N. Y.

Selective retrograde aortography is a method whereby radiographic visualization of the aorta and/or any of its branches is obtained. A catheter is introduced into the aorta via a peripheral artery (usually the common femoral) and its tip is maneuvered to the region to be visualized. Contrast medium is introduced rapidly through the use of a pressure injector. Multiple radiographic exposures are made in rapid sequence in order to record the passage of the opaque material. The technic is applicable to patients in all age groups.

We studied 17 patients selected because previous evaluation suggested an anomaly of the thoracic aorta. The smallest infant weighed 3.5 Kg. Three patients were younger than 6 months. Four more were under 2 years. Four were between 2 and 5 years, and 2 were aged 11 and 16 years. There was no mortality and insignificant morbidity.

In all patients, the diagnostic problem concerned the demonstration or exclusion of an abnormal communication between the aorta and another portion of the cardiovascular system. In 5 patients such an abnormal communication was excluded. In the remainder, the following lesions were identified: persistent truncus arteriosus, aorticopulmonary window, atypical patent ductus arteriosus, coronary arteriovenous fistula, congenital aortic regurgitation, and aortic regurgitation superimposed on an intracardiac congenital malformation. These entities have been grouped for convenience as "lesions of aortic integrity." The information needed was not obtainable with the same degree of certainty by any other diagnostic study. In 4

patients, the information was particularly valuable in decisions regarding surgery.

Hemodynamic Observations in Aortic Stenosis in Adults

Alvin J. Gordon, Howard L. Moscovitz, and Paul A. Kirschner, New York, N. Y.

Nine adults with aortic stenosis were studied by combined transbronchial and aortic catheterization. Simultaneous equisensitive pressure pulses were recorded across the aortic valve, together with continuous pressure differences and heart sounds.

Peak systolic gradients varied from 43 to 92 mm. Hg, mean ejection gradients from 42 to 76 and maximum ejection gradients from 64 to 102. The continuous pressure difference across the valve was characteristically the shape of an inverted V, the peak of which (maximum ejection gradient) coincided with the anacrotic notch on the aortic pressure pulse and the point of maximum amplitude of the diamond-shaped murmur.

When the catheter passed from left ventricle into aorta (antegrade) the aortic pressure pulse showed a prominent early systolic dip (Venturi effect) which was much less pronounced when recorded from the same site by the catheter passed to the valve via a peripheral artery (retrograde).

In withdrawal tracings from central aorta to peripheral artery, it was possible to trace the transformation of the early systolic dip into the anacrotic notch, which came to lie progressively higher on the upstroke of the aortic curve. Withdrawal tracings from aorta to left ventricle showed transitional beats ("washing phenomenon") in 2 patients with additional mild aortic insufficiency. In 1 patient, withdrawal tracings suggested supravalvular stenosis.

Measurement of the phases of the cycle confirmed that ejection was uniformly prolonged.

Intracardiac Surgery under Deep Hypothermia Without a Mechanical Oxygenator

Archer S. Gordon, Bert W. Meyer, and John C. Jones, Los Angeles, Calif.

Rapid extracorporeal cooling of blood by means of efficient heat exchangers has made possible prolonged intracardiac surgery without the use of a mechanical oxygenator. Detailed physiologic studies have been carried out on 60 dogs and 30 congenital cardiac patients during surgery with this technic. Animals have survived cooling to 5 C. and rewarming after 60 minutes of total circulatory arrest. Patients have been cooled to 9 C and successfully sustained 1 hour of circulatory arrest. Studies during cooling and rewarming have included: (a) simultaneous measurement of temperature in brain, heart, muscle, skin, rectum, esophagus, and superior vena cava; (b) oxygen consumption during cooling to temperature of 5 C.; (c) continuous recording of electrocardiograms, electroencephalograms, and blood pressure; and (d) acid-base balance as measured by frequent pH, CO_2, lactic acid, and pyruvic acid.

Lesions successfully operated with this technic include atrial septal defects, total anomalous pulmonary venous drainage, aortic stenosis, pulmonary valvular and/or infundibular stenosis, ventricular septal defects, and tetralogy of Fallot. The advantages of the method include: minimal mechanical equipment (2 pumps, 2 gravity reservoirs and a heat exchanger); small priming volume (1,200 cc. of blood); simplicity of operation; and an ideal surgical field, completely quiet and bloodless without the use of drugs or anoxic arrest.

There have been no instances of central nervous system damage in our experiences to date. Use of the temperature and oxygen-consumption studies reported here provides a clinical means for determining the safe period for circulatory arrest under deep hypothermia without brain damage or serious acidosis.

Disclosure of a Systematic Difference in Cardiac Output Values Determined by External Counting and Arterial Sampling Technics

Ralph J. Gorten, San Antonio, Texas, and J. Caulie Gunnells, Durham, N. C.

In previous comparisons involving the isotope–external counting method, determinations were not always performed simultaneously, isotope was injected into the antecubital vein, and favorable agreement was observed.

In 14 volunteer subjects, iodinated (I^{131}) serum albumin (antecubital vein) and blue dye (superior vena cava) were administered simultaneously. Cardiac output was determined at rest and following circulatory stimulation by external counting over the heart and by well counting and spectrophotometric analysis of arterial samples. The mean well counter minus dye difference was +8 per cent (+0.5 L./min., S.D. ±0.7) for resting values and +9 per cent (+0.8 L./min., S.D. ±1.4) after stimulation. The respective external counting–dye figures were +2 per cent (+0.1 L./min., S.D. ±0.9) and +5 per cent (+0.5 L./min., S.D. ±1.6).

A second group of 18 subjects was studied in the same manner except for femoral vein injection of isotope. Well counting–dye comparison revealed +9 per cent (+0.5 L./min., S.D. ±0.5) difference before and +4 per cent (+0.3 L./min., S.D. ±0.7) after stimulation. The main external counting–dye differences were +22 per cent (+1.2

L./min., S.D. ±0.6) and +23 per cent (+1.8 L./min., S.D. ±0.9) ($p < 0.01$).

To elucidate the mechanisms responsible for the significant and systematic discrepancies between external counting and arterial sampling technics with femoral injection as opposed to the antecubital site, certain factors were evaluated. This resulted in the following order of decreasing importance: streaming of isotope bolus during its early cardiopulmonary course, mixing problems caused by local venous spasm and junction with faster flowing blood, erroneous equilibrium values, undetected early recirculation, and lag in external counting instruments.

Correlation of Clinical and Physiologic Observations in Congenital Aortic Stenosis

Edward W. Green and Robert F. Ziegler, Detroit, Mich.

Retrograde left ventricular catheterization was combined with conventional right heart catheterization in 106 patients with clinical congenital aortic stenosis, ranging in age from 3 weeks to 25 years. Cineangiocardiography was used in selected cases. No complications have been encountered. Successful catheterization of the left ventricle was accomplished in 94 patients. Complicating lesions such as coarctation of the aorta, mitral stenosis, and pulmonic stenosis were demonstrated in 16 instances.

The purpose of this study was to correlate the clinical, electrocardiographic, x-ray, and physiologic data in order to determine the contribution of each observation to the final diagnosis.

Cases of mild to moderately severe aortic stenosis tended to show the typical aortic ejection murmur and thrill without the classic signs of left ventricular enlargement in conventional x-rays. Electrocardiographic evidence of left ventricular concentric hypertrophy in some cases consisted of increased positivity of left precordial T waves. The murmur of aortic stenosis was occasionally confused with other defects in small children.

The classic criteria of aortic stenosis such as dyspnea, syncope, angina, pulse pressure narrowing, and easily recognizable left ventricular enlargement on x-ray and the electrocardiogram occurred with regularity only in the most severe cases.

The clinical, x-ray, and electrocardiographic studies are usually adequate to diagnose congenital aortic stenosis; but they ordinarily require supplementation by retrograde left ventricular catheterization to determine the degree of stenosis and the importance of complicating defects before advising or withholding surgery.

Why Use the Monamine Oxidase Inhibitors in Treating Cardiovascular Disease?

George C. Griffith, Los Angeles, Calif.

The monamine oxidase (MAO) inhibitors occupy a unique place in the therapy of cardiovascular disease in that they not only provide effective prophylaxis against anginal pain in roughly 70 per cent of patients, but they also affect mood, drive and activity. Treatment with the MAO inhibitors must be individualized. The patient with psychomotor agitation or hyperactivity may become even more agitated and hyperactive if he receives the type of MAO inhibitor which ordinarily increases activity, unless he receives—in addition—a tranquilizing agent, such as one of the phenothiazines. Used in the wrong patient, several of the hydrazides—notable exceptions to the types which increase drive and activity—can intensify the syndrome of dullness, increased fatigue and lack of initiative. If the MAO inhibitor which meets the need of the individual patient is employed, considerable clinical improvement results, followed by elevation of mood. Continued close observation of patients under treatment with the MAO inhibitors is mandatory in order to abort side effects before they become troublesome and to insure the continuance of physical restrictions commensurate with the patient's cardiac status. If the patient is passing through a period of particularly difficult adjustment, the use of a MAO inhibitor with definite antidepressant action is of decided help.

Effect of Serotonin on Coronary Vascular Resistance and Myocardial Oxygen Consumption

Douglas M. Griggs, Jr., and Robert B. Case, New York, N. Y.

The effect of serotonin on coronary vascular resistance (CVR) was studied in the dog while coronary flow was maintained at a constant rate. Under this condition, any change in CVR is evidenced by a change in coronary perfusion pressure. Blood was delivered by an occlusive pump from the femoral artery through a rotameter to the left main coronary artery via a Gregg coronary cannula. Continuous recordings were made of mean coronary perfusion pressure, mean right atrial pressure, aortic pressure, and coronary flow. One ml. of a solution of serotonin in saline (concentrations from 1 to 30 μg./ml.) was injected into the perfusion circuit. The time of arrival of the injected material was signaled by a thermistor in the myocardium, so that the time of onset of the response could be related to the presence of the agent.

The results demonstrated a prompt fall in CVR when the drug reached the coronary circulation,

fore a change in heart rate or aortic pressure curred. The percentage decrease in CVR was lated to the dose administered. Myocardial oxygen consumption determined at the time of maximal fall in CVR, but before the onset of the peripheral action of the drug, showed no change om control values.

It is concluded that serotonin is a potent, benign coronary dilator.

ctors Governing the Efficiency of Stethoscopes

Dale Groom, Clarence S. Davis, and Wofford . Francis, Charleston, S. C.

Physicians vary remarkably in their ability to ear the fainter, less obvious murmurs of early valvular heart disease. Measurements of auscultatory thresholds demonstrate that differences in stethoscope efficiency and in levels of environmental noise are major determinants of audibility of a cardiovascular sound. Both factors can, in most instances, be modified to advantage.

Tests of 33 stethoscopes in current use revealed three fourths of them to be down 7 decibels or more in efficiency of sound transmission as compared to one of good design, and some to be down as much as 12 decibels (a ratio of 15 to 1). Only about one third of the stethoscopes tested could be considered adequate for cardiac examination. A more than 300 per cent average improvement in the stethoscopes was achieved by shortening them to an over-all length of 20 inches, replacement of soft or thin-walled rubber by plastic tubing of three-sixteenths inch internal diameter, and elimination of leaks at the ear-pieces, change-over valves and chest-pieces. Some of the instruments were improved many fold thereby. The total internal volume of a stethoscope, its frictional losses, the integrity of the acoustical seal between the body surface and the auditory canal, and the noise-rejection properties of its tubing are the chief considerations in design of a good stethoscope.

Application of these elementary acoustical principles—all of them independent of one's hearing acuity or professional experience—affords a practicable means of improving auscultatory proficiency.

ffect of Abnormal Ventricular Contraction Patterns on Ventricular Ejection

Abraham Guz, Julien I. E. Hoffman, R. Rolla otts, and William L. Weirich, San Francisco, lif.

The stroke volume of single right ventricular ats was studied in intact, conscious dogs with the lin electromagnetic flowmeter. When the core- s probe was implanted around the main pul- nary artery, bipolar myocardial electrodes were sewn onto the outer walls of both ventricles. Several days after recovery, rectangular electrical impulses of 0.15 msec. duration and of a voltage sufficient to produce ectopic beats (usually 5 to 10 volts) were delivered by a Grass stimulator. These beats occurred at varying times in the cardiac cycle. Spontaneous ectopic beats were also observed during epinephrine infusions.

Normal stroke volumes and flow patterns were found with markedly varying abnormal electrical (and, therefore, presumably mechanical) patterns of ventricular activation, provided that the ectopic beats came late in the cardiac cycle after normal P waves had been inscribed. Even slight encroachment upon the P wave caused some decrease in stroke volume. As the interval between the ectopic and the preceding normal beat shortened, the stroke volume decreased progressively.

Rapid pacing of the right or left ventricles reduced the stroke volume. The first normally activated beat after stimulation was stopped had a normal stroke volume only if a normal, fully inscribed P wave preceded it.

These findings suggest that the patterns of spatial activation of the ventricles do not influence ejection from the right ventricle unless they reduce its filling either by encroaching on the filling time or by interfering with atrial activity.

Myxoma of the Left Atrium: Report of Two Cases and Review of the Diagnostic Methods

Thomas E. Hair, Jr., Edward S. Orgain, Will C. Sealy, and Henry D. McIntosh, Durham, N. C.

Left atrial myxomas, although quite rare, commonly masquerade as rheumatic mitral disease. Any atypical feature suggesting a mitral lesion in a patient should arouse suspicion of a tumor, particularly those whose signs and symptoms are sudden in onset or present circulatory crises interspersed among periods of comparative good health. Variable auscultatory findings from day to day or complete alteration of murmurs upon change in body position should suggest the diagnosis.

Phonocardiographic study may substantiate discrepancies; however, electrocardiography or routine cardiac catheterization appear to be of little aid in making the differentiation. Symptoms out of proportion to left atrial size may have significance.

Two cases of left atrial myxomas, successfully removed at operation, are presented. Both patients exhibited atypical clinical features. In addition, the occurrence of periodic disparity in the degree of vascular engorgement in the 2 lung fields was strikingly present in 1 case and was very suggestive in the other. To our knowledge, the available literature has not commented upon this sign previously. Correct diagnosis was made

in 1 patient during operation and in the other, preoperatively, by cinecardioangiographic study.

With the newer diagnostic methods currently available, precise evaluation of cardiologic problems is possible. It appears that angiographic study is the only definite preoperative means of establishing the correct diagnosis. Resort to this measure will parallel the degree of clinical alertness and of suspicion aroused by any atypical features exhibited by the patient.

Atherosclerosis: Possible Role of Phagocytosis

Denham Harman, Omaha, Nebr.

Injury to endothelial cells enhances their phagocytic activity. Since atherosclerosis tends to develop in areas of mechanical stress, the possibility arises that lipid localization may be partly related to phagocytosis of lipoproteins by overlying endothelial cells. If so, lipoprotein surface properties may influence the rate of phagocytosis and hence the development of atherosclerosis.

The β-lipoprotein surface properties of 18 fasting human serums, as reflected by their paper strip electrophoretic mobility (EM), were studied before and after incubation at 37 C. (48 hours) under air and nitrogen, and an additional 18 in this manner plus in the presence and absence of copper acetate (9.1 mg. per cent). Serum free fatty acids (FFA) were also determined.

Incubation in air increased EM from 1.8 to 3.7 cm. (aver. 2.7) to 1.9 to 4.8 (aver. 3.3); under nitrogen the corresponding figures were 1.6 to 3.4 (aver. 2.6) and 1.9 to 4.0 (aver. 3.2).

Copper acetate increased EM from 1.9 to 4.1 (aver. 2.8) to 3.2 to 5.7 (aver. 4.3) in air; under nitrogen from 1.9 to 3.7 (aver. 2.7) to 2.5 to 4.5 (aver. 3.5).

FFA (μEq./L.) increased from 100 to 1,000 (aver. 520) to 1,400 to 3,800 (aver. 2,280) after incubation (independent of air, N_2, or copper); poor correlation between FFA and EM.

Incubation in air in presence and absence of copper (10 serums) had no effect on the low-density lipoprotein ultracentrifugal patterns.

Thus, it seems likely that serum lipoprotein surface properties change in vivo due, at least in part, to changes in FFA (ester hydrolysis, stress) and lipoprotein oxidation by O_2. Such changes may play a role in atherosclerosis by altering the rate of the postulated phagocytic activity of endothelial cells.

Phonocardiographic and Electrocardiographic Studies of Normal Newborn Infants: Evaluation of Their Use for Detection of Patency of the Ductus Arteriosus

Herbert S. Harned, Jr., and Ernest Craige, Chapel Hill, N. C.

Serial electrocardiograms and phonocardiograms were performed on 38 newborn infants to evaluate the use of these technics for detection of patency of the ductus arteriosus. Initial studies were done approximately 1 hour after delivery, and repeat studies 24 hours later and again before the fourth day of life.

Characteristically, the initial phonocardiograms revealed early systolic ejection clicks and no splitting of the second heart sound. Electrocardiograms showed QRS axis ranging from 90° to 180° and forward. The T axis ranged widely from −30° to 150°.

The phonocardiograms after 24 hours showed splitting of the second heart sound in half the subjects and persistence of the ejection clicks. Electrocardiograms revealed QRS axis positions similar to the initial studies, but many of the subjects showed striking posterior shifts of the T axis. In all subjects over 3 days of age, the T axis was markedly posteriorly directed.

Six subjects had systolic heart murmurs which were usually of low intensity and were noted in late systole on only 3 occasions. All but 2 of these murmurs disappeared after 24 hours, but 2 new murmurs appeared in other subjects.

Apgar ratings were high in all but 1 of the patients who developed a murmur. Of 4 babies with Apgar ratings below 5, only 1 developed a detectable murmur.

These observations are contrasted to those of other authors who have detected a high incidence of murmurs in the newborn infant.

Spontaneous Closing of Ventricular Septal Defects: Two Case Reports

Herbert S. Harned, Jr., and Richard M. Peters, Chapel Hill, N. C.

The possibility of spontaneous closure of muscular ventricular septal defects was indicated in a recent report by Evans, Rowe and Keith.

The following cases provide additional information that closure can occur. Partial closure of a membranous septal defect is shown in the first case.

A white male had been hospitalized 6 times for heart failure. Physical examination had revealed a loud, holosystolic, lower left sternal border murmur and mid-diastolic apical rumble. Cardiac catheterization at 6 months revealed a step-up of 4 vpc oxygen content between right atrium and ventricle, and RV systolic pressure of 100 mm. Hg. After the first 2 years, the patient improved and at 4½ years, at catheterization, the step-up between right atrium and ventricle was 1.0 vpc. Pulmonary arterial systolic pressure was 40 mm. Hg. The defect was believed large enough for

argical repair. At surgery a surprisingly small, robe-patent, membranous defect was found and he muscular septum was intact. After closure of he defect with 1 stitch, the murmur disappeared.

A girl aged 11 months showed a loud, holosystolic, left sternal border murmur, an apical diastolic rumble, cardiomegaly, prominent hilar shadows by x-ray, combined ventricular hypertrophy by electrocardiogram, and a 2.2 vpc step-up between right atrium and ventricle by catheterization. Her heart murmur gradually disappeared, the heart size and electrocardiogram became normal during the next 3 years. At 4 years, cardiac catheterization was normal.

Pulmonary Venous Obstruction in Infants with Anomalous Pulmonary Venous Drainage

Anna J. Hauck, Abraham M. Rudolph, and Alexander S. Nadas, Boston, Mass.*

The clinical picture of total anomalous pulmonary venous drainage below the diaphragm is well known and includes signs of pulmonary venous obstruction. However, it is less well recognized that the latter hemodynamic handicap may be observed frequently in infants with total anomalous pulmonary venous drainage above the diaphragm. The purpose of this report is to describe the physiologic findings in 9 infants with supradiaphragmatic drainage and to point out that pulmonary venous obstruction was found in all.

The patients' ages ranged from 17 days to 7 months. Cardiac catheterization revealed increased pulmonary venous pressure in all. In 5 infants, pulmonary blood flow was large. Anomalous drainage was via a "persistent left superior vena cava," and obstruction to pulmonary venous return was secondary to disparity between the large flow and the diameter and length of the venous channels through which pulmonary venous blood coursed. Two other infants in whom anatomic obstruction to pulmonary venous return was found at autopsy also had increased pulmonary venous pressure. In 1, a constricted area was seen in the "persistent left superior vena cava" which received the pulmonary venous trunk. The other patient had an unusual anomaly; pulmonary veins entered a vessel which coursed through the right lung where it was constricted by a bronchus before it entered the azygos vein. Finally, increased pulmonary venous pressure was observed in 2 infants in association with raised end-diastolic pressure of the right ventricle and congestive failure.

Studies of Ventricular Activation in Acute Myocardial Infarction

J. Julian Haywood, Ronald H. Selvester, and Warner J. Johns, Jr., Los Angeles, Calif.

The timed vectorcardiogram affords a sensitive method for the study of ventricular activation. In 120 patients with acute myocardial infarction, we have recorded a series of 3 or more timed vectorcardiograms, spatial vectorcardiograms and electrocardiograms during periods of 1 to 45 days' observation. Thirty-five patients died during observation, having had 1 to 3 studies. One third of the deaths were autopsied.

All patients had abnormal electrocardiograms and timed vectorcardiograms. Ventricular activation loops similar to those described by others were observed; we have expanded these observations and correlated distortions in activations with loss of forces in specific areas. Septal forces were frequently distorted when this could not be deduced from the electrocardiogram. Injury patterns and arrhythmias were better seen with the electrocardiogram; the abnormal timed vectorcardiographic activation produced by infarction remained stable through the period of observation. Prominence of the left atrial forces was correlated with the clinical appearance of congestive failure.

When intraventricular conduction defects were present in the electrocardiograms, the vectorcardiogram was particularly helpful in separating right and left bundle-branch-block activation loops from delayed activation produced by myocardial necrosis in other areas, as well as diagnosing infarction in the presence of typical bundle-branch patterns. When specific areas of infarction were deduced from the timed vectorcardiogram, more accurate anatomic localization was possible than with the electrocardiogram in the autopsied cases (75 per cent of 25 lesions in 10 autopsied cases, as against 50 per cent).

These methods may contribute much to the serial study of ventricular activation in patients with coronary heart disease.

Myocardial Blood Flow by Radiodilution Technics: Effect of Pressor Amines Administered during Hemorrhagic Hypotension

Walter S. Henly, Page W. Nelson, Malcolm B. Daniell, George P. Noon, and Michael E. De Bakey, Houston, Texas*

Myocardial blood flow may be recorded graphically in a simple physiologic preparation utilizing special radiodilution technics. A known concentration of iodinated (I^{131}) human serum albumin is injected at a constant rate into the left atrium, establishing a temporary equilibrium concentration of the isotope in the aorta and coronary arteries. If a venous reservoir of sufficient size has been inserted into the circulatory system of the laboratory animal, the venous return may be delayed to allow complete isolation of the coronary

component from the composite radiodilution curve of the right heart. Thus, by monitoring aortic and pulmonary arterial blood, simultaneous measurement of cardiac output and myocardial blood flow is possible. By gradually decreasing the cardiac input, a controlled hypotensive state is produced. The resulting decrease in myocardial blood flow closely parallels the drop in cardiac output and mean arterial blood pressure. With the cardiac input maintained constant at a low level, the effect of commonly used pressor amines on coronary blood flow has been studied by this technic. Coronary flow may increase from a normal of 5 to 10 per cent of cardiac output to 25 to 50 per cent, depending on the drug and quantity administered. Epinephrine and levarterenol continue to increase coronary flow exponentially as the blood pressure rises. Phenylephrine initially produces an increase in coronary flow greater than expected from a rise in blood pressure alone. However, this effect is lost as the blood pressure approaches normotensive levels.

Sequential Changes in the Development of the Electrocardiographic Pattern of Left Ventricular Hypertrophy

Lawrence M. Herman, Los Angeles, Calif., Mary M. Cosby, and Richard S. Cosby, Pasadena, Calif.

Classic electrocardiographic theory suggests that the pattern of left ventricular hypertrophy develops gradually and continuously from the norm. This implies, first, that the direction and magnitude of the QRS vector changes continuously with time and, second, that changes in the ST-T vector are secondary to changes in the QRS vector. Discontinuous changes, on the other hand, would imply that other factors such as superimposed coronary artery disease with peri-infarction block, etc., would be dominant in the development of the pattern. This problem is investigated by means of a long-range study of the evolution of the pattern in selected cases.

This study consisted of: (1) 19 patients selected from among 400 who had died of hypertensive heart disease at a large general hospital; the patients selected had initial normal electrocardiograms and later the pattern of left ventricular hypertrophy; (2) 21 patients with similar electrocardiographic criteria from a series of 500 private subjects with a diagnosis of hypertensive heart disease.

Results: 1. Changes in the electrocardiographic pattern of left ventricular hypertrophy in this series occurred in sudden unpredictable steps rather than by gradual continuous progression. In fact, no patient could be found to illustrate the continuous increase in height of R and increasing depth of T which would correspond to classical theory. 2. In general, T-wave changes occur concomitantly with changes in QRS, suggesting their secondary nature; criteria to distinguish primary from secondary T-wave change are described. 3. The precordial lead electrocardiogram is more sensitive to the changes of so-called left ventricular hypertrophy than are classical leads. In many instances, increase in voltage and T-wave change occur in the horizontal plane before there is any change whatever in the frontal plane. One is led to conclude that degenerative (atherosclerotic?) changes must be invoked to explain fully the "hypertrophy" patterns.

Vascularization of In Situ and Intraocularly Transplanted Atheromatous Plaques in Rabbits

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Vascularization of atheromatous plaques is commonly believed to occur either late in atherogenesis, or to occur early and perhaps play an important role in extension of the plaques as well as in their formation. Observations in situ and intraocularly transplanted plaques in rabbits, and on a limited amount of human material, suggest that in general both views may be true, but in a more restricted sense vascularization should be included with the processes occurring early in atherogenesis.

A well developed plaque in the rabbit is seldom of uniform composition. The deeper and more central parts generally are more fibrous or degenerative compared with superficial and circumferential parts which are more cellular, containing numerous foam cells. Vascularization of such a transplanted plaque apparently is restricted to the more cellular portions, since no vessels have been found in the degenerative areas.

In the rare instances when small vascularized areas of old atheromatous plaques in situ were seen in the aortas of rabbits several months after their production, the vessels were limited to areas containing foam cells. The same relationship appears to exist in the human arteries examined.

Since there seems to be a definite relationship between foam cells and vascularization of plaques, the process should more properly be considered as one occurring early in plaque formation, but which may occur later in old plaques whenever accumulations of foam cells are present.

Direct Records of the Electrical Activity of the Specialized Conducting System Obtained through Chronically Implanted Electrodes

Brian F. Hoffman, Jackson H. Stuckey, Albin A. Bagdonas, and Robert S. Venerose, Brooklyn, N. Y.

Direct records of the electrical activity of various parts of the specialized conducting system previously have been obtained during acute experiments. The present studies were undertaken to determine whether or not the technics employed introduced any important variables in the data obtained from such acute experiments. Plastic electrodes containing multiple contacts have been attached, during total cardiopulmonary bypass, to the epicardium of the atria and ventricles and to the endocardium over the bundle of His and peripheral Purkinje-papillary muscle junctions. Records have been obtained through these electrodes for periods up to 6 weeks after implantation. Comparison of pre- and postoperative electrocardiograms and direct studies of the electrical activity of the His bundle and Purkinje fibers has shown no evidence of impaired conduction or tissue injury due to electrode implantation. Conduction velocity in the His bundle and peripheral Purkinje system in chronic experiments agrees with observations made during acute experiments. Direct records obtained through chronically implanted electrodes have been employed to study local changes in conduction in the His bundle and Purkinje fibers during arrhythmias, hypoxia, and the action of autonomic agents.

Stroke Volume and Cardiac Output Measurement in the Intact Animal with an Electromagnetic Flowmeter

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Continuous observations were made on the right ventricular stroke and minute volumes of intact, conscious dogs, using a modified Kolin-type 400 cycle sine-wave electromagnetic flowmeter with the miniaturized coreless probe placed around the main pulmonary artery. Studies were done after complete recovery.

A constant zero flow base line was obtained by injecting acetylcholine and causing cardiac arrest for 3 to 7 seconds. The flowmeter was calibrated in anesthetized dogs by recording flow simultaneously with dye-dilution curves over a range of cardiac outputs produced by isoproterenol infusions. With a wide range of cardiac frequencies and maximum velocities, the areas under the flow curves per minute showed a close linear correlation with cardiac output; the regression line passed through zero. One week later the calibration was unchanged. Since the instrument measures velocity of blood flow through a constant cross-sectional area, this calibration is valid for volume flow and velocity.

This technic was used to measure, in conscious animals, sudden and longer-lasting changes in stroke and minute volume, e.g., changes during feeding, with different postures, and during respiration. The stroke volume and maximal velocity were greater during inspiration, particularly with rapid breathing, and during barbiturate anesthesia when changes up to 50 per cent of stroke volume occurred. During acetylcholine-induced cardiac arrest, inspiration moved nearly as much as the stroke volume out of the right ventricle. By contrast, the stroke volume fell when positive pressure was applied to the airway. The time course of this fall and its recovery after restoration of normal airway pressure suggested that the change was mediated through alterations in venous inflow.

Some Effects of *l*-Norepinephrine during Total Body Perfusions in Dogs

Robert P. Hohf and George C. Sutton, Evanston, Ill.

l-Norepinephrine was administered to dogs after establishment of stable total body perfusions with bypass of the heart and lungs. With the vascular bed independent of the cardiac output, the perfusion rate of the arterial pump was kept constant. Then the effects of the vasopressor were studied by continuously recording the changes in weight and blood volume of the animals, the venous return flows, and the aortic and inferior vena caval pressures. In a group of 7 dogs, a single abrupt dose (.2 mg.) of *l*-norepinephrine was administered, and in a second similar group a continuous infusion (4 mg. in 500 ml. of saline at 60 to 90 drops/min.) over 15 to 60 minutes was given.

The results of a single dose were consistent. The caval pressure decreased in the first 5 minutes and rose essentially to its original level in 5 to 10 minutes. Weight of the animals dropped for 5 minutes and climbed progressively thereafter, exceeding the initial weight. Blood volume changes paralleled those of weight. Venous return flows did not follow a pattern, sometimes increasing or decreasing slightly, or not changing.

When a prolonged infusion of *l*-norepinephrine was given, the early results were similar. However, as the vasopressor effect continued, the responses changed. The caval pressure, body weight and blood volume all rose steadily, and after the infusion was stopped, the rate of increase accelerated. The following interpretations are made:

1. *l*-Norepinephrine causes constriction of both arterioles and venules resulting in an early decrease in the total vascular volume, but as the constriction continues, the venous effect produces pooling in the capillaries.

2. *l*-Norepinephrine is not an effective agent for increasing venous return in extracorporeal circulation.

3. The vasopressor may be harmful in perfusions because of vasodilatation and increased pooling following its use.

Effects of Triparanol on Body Cholesterol and Sterol Metabolism

William Hollander and Aram V. Chobanian, Boston, Mass.

The present study was undertaken because of reports that sterols other than cholesterol appear in the blood during triparanol therapy.

Our metabolic studies indicate that triparanol produces: (1) a highly significant and sustained reduction in serum cholesterol; (2) a significant decrease in the total sterols of the blood, but to an extent less than the reduction of serum cholesterol; (3) a significant decrease in the "miscible pool" of cholesterol as determined by the disappearance curves of intravenously administered C^{14}-labeled cholesterol; (4) a significant decrease in the "total sterol pool" as indicated by serum specific activity of the total sterols as well as by dibromide purification of serum cholesterol; (5) a significant decrease in the amount of both cholesterol and total sterol that is turned over per day; and (6) a significant reduction in the formation of radioactive sterol from administered C^{14}-labeled acetate or C^{14}-labeled mevalonic acid.

These metabolic changes caused by triparanol revert to control values after withdrawal of the compound. Triparanol is effective in reducing both serum cholesterol and the "miscible pool" of cholesterol in man. The compound also reduces significantly the total sterol content of the blood as well as the "total sterol pool." These effects appear to result from an interference with the biosynthesis of cholesterol.

Electrolyte and Water Metabolism in Malignant Hypertension

William Hollander and Aram V. Chobanian, Boston, Mass.

The present studies were undertaken to determine whether alterations of electrolyte and water metabolism are present in "malignant" hypertension.

As compared with normotensive controls, patients with malignant hypertension (as those with uncomplicated essential hypertension) had an increased capacity to excrete sodium, as indicated by the rate of excretion of an intravenously administered sodium load. However, in contrast to control and uncomplicated hypertensive subjects, malignant hypertensive patients without clinically detectable peripheral edema had significant increases in total exchangeable sodium (Na^{24} space) and extracellular fluid volume ($S^{35}O_4$ space), and an associated prolonged decholin circulation time. Similar findings were observed in hypertensive subjects with mild congestive heart failure, or with primary hyperaldosteronism. However, total exchangeable potassium was only slightly decreased in malignant hypertensives, and never to the severe degree observed in primary hyperaldosteronism. The blood pressure lowering effect of the aldosterone antagonist, spironolactone, in malignant hypertensives was no greater than that found in other types of hypertensives.

These findings indicate that the increases in body sodium and extracellular fluid volume found in malignant hypertension may be a manifestation of preclinical congestive heart failure, which may also account for the marked increase in aldosterone excretion and secretion reported by other workers in this syndrome.

How Irregular Is the Ventricular Response in Human Atrial Fibrillation?

Leo G. Horan, New Orleans, La., and Jack C. Kistler, Jackson, Miss.

A total of 47 single-lead electrocardiograms varying in length from 442 to 1,412 beats were recorded in 17 patients with atrial fibrillation. From careful measurement of the R-R intervals, distribution curves were plotted of the percentage of beats for each R-R interval length. Serial comparison of the configuration of frequency distribution curves of the ventricular interval was made in individual patients and all of the curves were studied as to relation to mean ventricular rate.

There were 28 curves with a single peak varying from the tall and narrow with a short mean interval in the untreated to the short and broad with a longer mean interval in the digitalized. However, there were 11 double-peaked curves, 5 plateau-like curves, and 3 long, low, extremely flat curves. Frequently, serial change was observed in configuration from tall, narrow unimodal through bimodal to short, broad unimodal curves in patients undergoing digitalization with reversal upon withdrawal of digitalis or administration of atropine. The low, flat curves appeared during digitalis intoxication.

These observations demonstrate that the ventricular response in atrial fibrillation is not random, and further indicate the occurrence of some form of concealment of impulse in the A-V node as suggested by several current hypotheses.

Effect of Intracavitary Carbon Dioxide on Surface Potentials in the Intact Canine Chest

Leo G. Horan, Harry F. Yoffee, and Robert J. Andreae, New Orleans, La.

Lissajou patterns derived from pitting front and back MeFee grids against central terminals were recorded with other pertinent electrocardiographic data in 20 supine, anesthetized mongrel dogs. Correlations were made between the Lissajou patterns and the anatomic measurements of ventricular weight, volume, and surface area. A check on the relative electrical contribution of each ventricle was made by transiently replacing the blood in each cavity with a nonconducting medium (CO_2) via cardiac catheter during recordings.

Distinctive reproducible patterns of reduction of amplitude in Lissajous, vector loops, and leads were found during CO_2 instillation. Especially prominent diminution of potential recordings was noted during early and late depolarization for the CO_2-infused right ventricle and during mid-depolarization for the CO_2-infused left ventricle. Care was taken to distinguish between immediate effects of increased resistivity in the left cavity and subsequent effects of CO_2 embolization to the coronary arteries.

These experiments provide a means of separation in great part right and left ventricular electrical contributions to surface recordings in the dog with an intact chest.

Effect of Tobacco Smoking on the Clotting Process in Man as Measured by Thrombelastography

Orville Horwitz and Donald S. Waldorf, Philadelphia, Pa.

The thrombelastograph is an apparatus which measures, under constant and reproducible conditions, the elastic changes of a thrombus during the whole coagulation process. It determines graphically the time at which a clot starts to form, the rate at which it forms once it has started, and its continued tensile strength and elasticity.

Thrombelastograms were recorded on 10 normal fasting subjects, 5 men and 5 women, ranging in age from 21 to 44 years, before and after smoking 1 standard length nonfiltered cigarette of high nicotine content. There was no change in r, the time, measured in minutes, at which the clot *starts* to form. There was, however, an increase in the tensile strength of the clot as well as in the rate of clot formation, and invariably an increase in the MA/k value. The MA/k average increased from 7.8 to 14.7 (89 per cent). MA, measured in millimeters, varies directly as the tensile strength of the clot, and k, measured in minutes, varies inversely as the rate of clot formation. No significant changes occurred in the thrombelastograms of the same fasting subjects before and after *not* smoking.

Apparently, tobacco smoking does not influence the time at which a clot *starts* to form, but does increase the tensile strength and the rate of formation of clots.

Clinical Appraisal of the Vectorcardiogram in 207 Cases of Myocardial Infarction (Frank System)

Paul G. Hugenholtz, Claude E. Forkner, Jr., and Harold D. Levine, Boston, Mass.

The accuracy of electrocardiographic diagnosis of old myocardial infarction varies between 25 and 75 per cent in autopsied series. It has been contended that the vectorcardiogram is more accurate. Even greater precision is promised with the use of Frank's corrective lead system.

Of 207 cases analyzed, 125 met rigid clinical criteria for the diagnosis of old myocardial infarction. In 28, this diagnosis was confirmed at autopsy. The electrocardiogram was completely correct in 74 of the 125, while the vectorcardiogram was completely correct in 121. The electrocardiogram indicated multiple infarctions, found at autopsy, in 5 of 18 cases, whereas the vectorcardiogram did so in 14. The electrocardiogram completely failed to diagnose infarction in 13 cases and gave only questionable evidence in another 20 cases. The vectorcardiogram was correct in all of these. In no case did the electrocardiogram show infarction when the vectorcardiogram was negative. A false positive diagnosis of anteroseptal infarction could be made by electrocardiogram and vectorcardiogram in 3 cases of "giant right atrium."

In multiple infarctions, study of the direction of rotation of the sagittal plane loop often permitted recognition of a second infarct even when other vectorcardiographic evidence for this was lacking. With definite diaphragmatic infarction, counterclockwise rotation of the sagittal plane loop is expected, but clockwise rotation indicated concomitant anteroseptal or anterolateral infarct. Similarly, with established anteroseptal infarct, counterclockwise rotation is the rule in the sagittal plane, but clockwise rotation pointed to coexistent diaphragmatic infarct. In specific examples, these relationships were not obvious in the routine electrocardiogram.

Patient with Mitral Stenosis and Mild Symptoms

Paul G. Hugenholtz, Samuel W. Stein, Thomas J. Ryan, and Walter H. Abelmann, Boston, Mass.*

The predictability of mitral valve size from the severity of symptoms and degree of disability was investigated by clinical and hemodynamic evaluation of 49 patients with mitral stenosis.

Five fell into class 1 (no symptoms) and 22 into class 2 (mild nonlimiting symptoms). Twenty-two patients in class 3 (severely disabled by dyspnea,

fatigue, and intermittent fluid retention) served for comparison. Ten of the 27 patients with mild symptoms had mitral valve areas below 1.0 cm.^{2} compared with 14 of the 22 in class 3.

When patients in class 2 with valve areas less than 1.5 cm.^{2} were compared to those in class 3 with similar valve areas, they tended to have lower mitral valve flows and left atrial pressures. Moreover, the cardiac index in both classes was significantly lower than in normal patients (2.8 versus 3.7). On the other hand, pulmonary arteriolar resistance and pulmonary arterial pressure were strikingly elevated in class 3, while normal in class 2 ($p < 0.01$). In both classes the expected correlation between left atrial pressure, mitral valve gradient, mitral valve flow, and mitral valve area was demonstrated.

It appears that decreased cardiac output occurs before serious clinical symptoms have developed and is not related to changes in cardiac rhythm, rate or pulmonary resistance. Indeed, clinical symptoms often fail to predict mitral valve size accurately. However, the division by clinical data into class 2 and 3 is justifiable and is paralleled by the differences in pulmonary vascular resistance between the 2 groups.

The Hydrogen-Platinum Electrode System in Detection of Cardiac Shunts

Albert L. Hyman, Edward S. Hyman, Anthony Quiroz, and James Gantt, New Orleans, La.

Advances in cardiovascular surgery indicate the need for more accurate diagnostic measures in preoperative evaluation. The Clark technic employs changes in oxidation potential of blood, produced by a single breath of hydrogen, and indicated by a platinum electrode. This technic was modified by introduction of a high-impedance circuit, and extended by constructing platinum electrode stylets for Cournand and Henry indwelling arterial needles, and open lumen cardiac catheter electrodes. Simultaneous recordings were obtained from an intracardiac electrode catheter and systemic artery simultaneously in 34 patients with intracardiac shunts by using a single breath of hydrogen. The method identified the shunt in each patient, as did the double catheter cardiogram dye technic, while the oxygen step-up method failed in 4 small shunts.

Hydrogenated saline or blood injected into the right heart is not detected in the systemic circulation after passing through the lungs. Right-to-left shunts are able to be detected with the arterial stylet.

Injecting hydrogenated blood or saline downstream and detecting it upstream with an electrode catheter readily detected valvular regurgitation.

Subclavian pulmonary artery anastomosis was produced in 6 dogs, and an inflatable Jacobson cuff was fitted about the subclavian artery. After recovery, the cuff was distended to occlude the vessel, and the hydrogen, double catheter dye, and oxygen technics were used to detect the shunt as the cuff was deflated in stages. The hydrogen readily detected the shunt before the dye or oxygen technics, or the appearance of a murmur.

Vasomotor Response of the Vital Organs during Cardiac Arrhythmias

David W. Irving and Eliot Corday, Los Angeles, Calif.

The blood flow of the intact carotid, renal, and mesenteric arteries of the dog was measured during arrhythmias with the new electromagnetic flowmeter and integrator-computer apparatus. This new technic allows the accurate measurement of blood flows without cutting or cannulating the blood vessel, so that the vasomotor apparatus is preserved.

Each organ has a specific vasomotor response during and immediately following various cardiac arrhythmias such as atrial and ventricular premature systoles and atrial tachycardia and fibrillation. The vascular resistance of the kidney rose markedly and persisted for at least 1 hour following termination of an arrhythmia. The mesenteric circulation appeared to be the most labile; the sudden increase in vascular resistance, although of large magnitude, was of brief duration. The resistance of the cerebral circulation increased slightly during arrhythmias and was intermediate in duration.

The circulation of the brain, kidney, and gastrointestinal tract is affected by the cardiac arrhythmias because of the vasomotor response of the target organ and a reduction in the cardiac output.

Angiotensin Therapy of Circulatory Failure in Man

Benjamin Jablons, New York, N. Y., Erlinda G. de Castro, Manila, Philippine Islands, Vilert Vichayanonda, Bangkok, Thailand, Paquita E. Manulat, Cebu, Philippine Islands, and Loreto S. Santiago, Manila, Philippine Islands

Synthetic angiotensin, 5-valine octapeptide, therapy was studied in 15 males and 4 females, aged 29 to 86 years, 7 in complete circulatory collapse (group A), 7 hypotensive from shock and other causes (diastolic 60 mm. Hg or below) (group B), and 5 normotensive. Angiotensin was administered in doses of 0.5 mg. in 20 ml. or 1,000 ml. 5 per cent dextrose saline intravenously, or in 60 ml. intramuscularly. Blood pressure rose in from 2 to 5 minutes in the hypotensive and normotensive

groups, the rise varying directly with increasing and decreasing amounts administered. In group A, blood pressure response was demonstrable only 30 to 60 minutes after angiotensin infusion was begun. (In group A, 2 patients showed no response to doses in excess of 50 μg./minute.) Four of 7 in complete circulatory collapse survived after continuous angiotensin therapy for 12 to 48 hours. One patient, after initial recovery, died of uremia 7 days later. Deaths in this and other groups were unrelated to angiotensin administered. No local reaction followed intramuscular injection or extravasation. Side effects were only facial flushing in 3 and abdominal cramps in 1. Angiotensin was compared with norepinephrine in 5 cases. In 4, angiotensin was equipotent in one-eighth the amount; in the fifth, norepinephrine was ineffective, angiotensin increased the blood pressure by 40 mm. Hg systolic and 40 diastolic. Angiotensin is a potent vasoconstrictor agent, with minimal side effects, with a protracted effect in many of the patients studied.

Angiotensin Skin Test in Normotensive and Hypertensive Humans

Benjamin Jablons, New York, N. Y., Paquita E. Manulat, Cebu, Philippine Islands, Ein S. Hahn, Seoul, Korea, Panya Nakvanich, Bangkok, Thailand, and Rosario C. Salvo, Manila, Philippine Islands

The local effect of intracutaneous administration of standard amounts of synthetic angiotensin was studied in 11 males and 16 females, aged 50 to 80 years. Twelve were normotensive and 15 were hypertensive. Angiotensin, 0.1 ml. of a dilution of 0.5 mg./1,000 ml. normal saline, was injected intradermally in the forearm and readings were taken at 5-minute intervals for a maximum of 3 hours. Wheals were produced in most instances with characteristic areas of blanching which were circular and sharply defined. Of the 12 normotensive subjects, 2 had little or no blanching; in 7, the blanched area faded after 10 minutes; in 2 blanching faded after 30 minutes, and in 1 blanching persisted for 60 minutes. In 15 hypertensives, blanching persisted for 30 minutes in 3; for 60 minutes in 5; for 120 minutes in 3, and for 180 minutes in 3. One failed to show blanching. Thus, in 9 normotensive subjects (75 per cent), area of blanching faded within 10 minutes, and in 14 hypertensive subjects (93.3 per cent), blanching persisted for 30 to 180 minutes. Necrosis or tissue damage was not observed. Control injections with normal saline only produced no blanching.

The above results suggest that hypertensives are more sensitive to the vasoconstrictor effect of intradermal injection of angiotensin than normotensives, and this test may be of additive value in differential diagnosis.

Microvascular Surgery: A New Horizon in Coronary Artery Surgery

Julius H. Jacobson, II, Donald B. Miller, and Ernesto Suarez, Burlington, Vt.

Results of vascular surgery have been uniformly poor in vessels below 4 mm. in diameter. Technics have now been developed for performance of vascular anastomoses under the dissecting microscope. Far greater precision is obtained. One has the choice of a lens-to-subject distance of 8 or 12 inches. The actual anastomosis is carried out under 10 to 25 magnifications. No. 7-0 atraumatic silk is used, and still finer materials are being developed.

One can tie knots so that intimal edges almost exactly coapt. Bits of adventitia not visible to the naked eye can be removed from the suture line. A 3 mm. anastomosis requires 20 to 25 stitches. These are necessary because there is no eversion, inversion, or bunching-up of the suture line which provides hemostasis with gross technics.

One hundred per cent patency has been obtained in 26 autogenous replacements in dog and rabbit carotid arteries measuring between 1.4 and 3 mm. in diameter. Highly promising work is in progress on replacement and shunting of the dogs' coronary arteries.

Myocardial Infarction and Atrial Arrhythmias: Clinical, Pathologic, and Experimental Studies

Thomas N. James, Detroit, Mich.

It has long been recognized that atrial arrhythmias beginning during an acute myocardial infarction are a bad prognostic sign, at least partly due to the resultant decrease in cardiac output. The present study was undertaken to learn more of the mechanism by which these atrial arrhythmias are produced.

The hearts of 11 patients who died of acute myocardial infarction, and in whom recent atrial arrhythmias were an important problem in their clinical course, were studied. Careful dissection of the atrial blood supply and the artery to the sinus node was performed in each heart; occlusions in a main coronary artery were noted as to whether they were proximal or distal to the origin of the sinus node artery. Serial sections were made of the sinus node for microscopic study. In 10 of the 11 cases, the main coronary artery was occluded proximal to the origin of the sinus node artery, and there was histologic evidence of infarction of the sinus node.

Experimental production of sinus node infare-

tion in dogs is difficult and results have not been consistent. Simple ligation of the sinus node artery produces no characteristic changes in rhythm. Additionally lowering central aortic blood pressure results in the onset of atrial arrhythmias in about half the animals studied, but does not result in the exact histologic changes in the sinus node found in humans.

A Sampling Study of Blood Pressure Levels in White and Negro Residents of Nassau, Bahamas

Benjamin C. Johnson and Richard D. Remington, Ann Arbor, Mich.

Previous reports from the Bahamas suggested that people in this area demonstrated unduly high blood pressure levels, suggesting possible environmental or genetic factors. Of particular note was the relatively high salinity of the water supply.

The study was designed as a true population study utilizing modern sampling technics. This method made possible comparisons by race, sex, age, in as precise a manner as possible. Over 3,000 persons were studied, with a high proportion of sample completion. Findings were:

1. Definite race differences were seen. For the Negro, mean systolic pressures increase with age in a regular, linear fashion from the youngest to the oldest. In the white race, mean systolic pressures show a leveling, or plateau effect, during early adult years, after which upward trend is resumed. Diastolic pressure means also show a definite racial difference, Negroes likewise having higher mean levels.

2. Sex differences were similar for both races, with definitely lower mean pressures being recorded for women between puberty and menopause than for men of similar age, and the reverse relationship beyond this age.

3. Comparison with other population studies showed that in regard to progression of systolic and diastolic blood pressure with age for a given race and sex, the Negro and white races were not greatly different from their racial counterparts studied elsewhere in the world (including a study of Negroes in a low-salt area). These findings tend to cast doubt on the role of sodium as an enhancing factor in etiology of hypertension in Negroes.

Multiple Occurrence of Congenital Heart Disease in Ten Families

John L. Johnson, Los Angeles, Calif.

Families observed between 1951 and 1960 involved 60 individuals as members of the immediate families, with 22 members being affected. The earliest reported example was in 1818, since then 150 to 200 families have been reported. In this report, 2 families have only males involved; 6, females; and 2 were mixed. Seven families had 2 or more siblings involved, and 3 families had siblings and a parent. Three families have patent ductus arteriosus; 2, ventricular septal defect; 2, atrial septal defect; 1, pulmonary stenosis; 1, coaretation and pulmonary stenosis; and 1, tetralogy of Fallot.

Patent Ductus Arteriosus:

Q family—mother, father and 8 children; 2 siblings affected, clinical and surgical proof.

S family—mother, father and 10 children; 2 siblings affected, clinical and surgical proof.

K family—mother, father, 3 children and an aunt; father, aunt and daughter are affected; clinical, and in child, laboratory and surgical proof.

Atrial Septal Defect:

P family—mother, father and 2 children; clinical, laboratory and surgical proof.

B family—mother, father and 3 daughters; mother and daughters are affected, clinical, laboratory and surgical proof.

Pulmonary Stenosis:

P family—mother, father and 3 daughters; the daughters are affected, clinical, laboratory and surgical proof.

Tetralogy of Fallot:

L family—mother, father and 3 children; 2 affected siblings are twins, clinical proof.

Ventricular Septal Defect:

C family—mother, father and 2 children; daughters are affected, clinical, laboratory and surgical proof.

M family—mother, father and 2 daughters; both daughters are affected, clinical and laboratory proof.

Coaretation and Pulmonary Stenosis:

C family—mother, father and daughter; father and daughter are affected, clinical and operative proof.

Selective Left Heart Cinecardioangiography in the Diagnosis of Acquired Heart Disease

Walter E. Judson, Eugene C. Klatte, and Nancy H. Rausch,† Indianapolis, Ind.

Selective cinecardioangiography has been established as a valuable diagnostic technic in the preoperative evaluation of congenital heart disease. Our experience has shown that it is also a valuable tool in the work-up of patients with acquired heart disease. Differentiation and quantitation of predominant stenosis or regurgitation in mitral and aortic valvular disease by hemodynamic alterations and indicator-dilution curves have not been invariably successful. Selective left heart cinecardioangiography provides visual evidence of the dynamic function of the myocardium, anatomic status and mobility of the valve leaflets, and an

estimate of the degree of competency of the atrioventricular and aortic valves.

Using the Seldinger technic, a polyethylene or Teflon catheter with a terminal "pigtail" configuration and multiple side holes is introduced into the femoral artery by percutaneous needle puncture and guided fluoroscopically into the root of the aorta where, by careful manipulation, the coiled end can be advanced across the aortic valve into the left ventricle. In over 80 patients, selective injections of contrast material have been made into the left ventricle and the ascending thoracic aorta with the distribution of the radiopaque material monitored by the aid of an image intensifier and recorded by a 16 mm. high-speed, motor-driven cine camera. With the injection into the left ventricle or central aorta, mitral or aortic regurgitation can be semiquantitated by the reflux of the contrast material through the incompetent valves.

In experimental and clinical material a comparison of the relative value of left atrial and aortic pressure tracings and left heart cinecardioangiography has been performed. The purpose of this paper is to present the technical factors and results of this study.

Urine Serum Glutamic Oxalacetic Transaminase Activity in Acute Myocardial Infarction

Robert B. Kalmansohn and Richard W. Kalmansohn, Los Angeles, Calif.

An attempt was made to establish the method and normal levels for the determination of urine glutamic oxalacetic transaminase (UGOT) activity and to evaluate these levels in patients with acute myocardial infarction. UGOT levels were run on 39 controls with no evidence of acute disease; only 1 determination was over 9 units (Karmen), the average determination being between 4 and 5 units. Accordingly, it was felt that any level over 9 could be considered abnormal. The urine pH and specific gravity did not appear to influence the result; however, the activity gradually disappeared after 30 minutes of standing at room temperature or in a refrigerator. Daily UGOT determinations were made in 15 consecutive patients with acute myocardial infarction proven by electrocardiograms and serum indices of myocardial necroses. All 15 patients had elevated UGOT levels ranging from 17 to 46 units and persisting for a minimum of 3 days. The height of the UGOT levels was not particularly correlated with the height of the SGOT levels, but the serum and urine levels remained elevated about the same length of time. This is an additional method of evaluating myocardial necrosis which is easy to perform and does not require multiple venipunctures.

Anomalous Connection of Pulmonary Veins: Clinical Variants

Robert B. Kalmansohn, James V. Maloney, Jr., and Richard W. Kalmansohn, Los Angeles, Calif.

Two patients with partial transposition of the pulmonary veins who presented unusual anatomic patterns were studied.

The first patient was a 10-year-old white boy with the history of a heart murmur since the age of 9 months and with clinical evidence of advanced left-sided congestive heart failure; he presented the classical murmur of patent ductus arteriosus and showed evidence of marked right ventricular enlargement (by physical examination, x-ray, and electrocardiogram). At thoracotomy, a small, widely patent ductus arteriosus was found; aortic and pulmonic pressures were approximately equal. The patent ductus arteriosus was ligated and divided. In addition, an anomalous pulmonary vein was found draining the left lobe and lingula to the innominate vein; this anomalous vessel was transposed to the atrial appendage. Postoperatively the patient has done well, with no evidence of heart failure, disappearance of the murmur, and marked decrease in the right ventricular enlargement.

The second patient was a 12-year-old white boy who presented findings consistent with the ostium secundum type of interatrial septal defect. At surgery, the inferior pulmonary veins from both lungs were found to drain into a fifth chamber behind the right atrium, which emptied in turn into the right atrium. With the aid of a pump oxygenator, the anomalous veins were transposed to the left atrium, with apparent restoration of the physiologic state.

Unusual Aspects of Ventricular Parasystole

Daniel E. Kaplan and Alfred Pick, Chicago, Ill.

A parasystolic rhythm of ventricular origin is usually a manifestation of heart disease in an older person. A slow ectopic center operates side by side, but out of phase, with the faster sinus pacemaker, regular impulse formation in each of the 2 centers being maintained by mutual "protection" of one center from the impulses of the other. In the electrocardiogram, this is then manifested by an undisturbed sequence of sinus P waves, while the regular ventricular action is periodically disturbed by premature beats with widely differing coupling intervals, separated from each other by longer or shorter "interectopic" distances reducible to a common denominator. Three cases of proven ventricular parasystoles have been studied with deviation from these usual features in that the disturbance occurred in young persons (aged 12, 13 and 25 years respectively),

in 2 without demonstrable heart disease, in association with a marked sinus arrhythmia. As a consequence of the latter: (a) the ectopic center discharged, temporarily, in phase with the sinus pacemaker with the result of ventricular group beating (bigeminy or trigeminy), with each parasystolic beat "coupled" to a sinus beat; and (b) slower phases of sinus activity permitted backward spread of the ectopic impulses through the A-V junction with the result of retrograde activation of the atria and premature extraneous discharge of the sinus node.

Effects of pH and P_{CO_2} on the Sensitivity of Purkinje Fibers to Digitalis

Joannes H. Karis, Merel H. Harmel, and Brian F. Hoffman, Brooklyn, N. Y.

Transmembrane resting and action potentials have been recorded from single Purkinje fibers in false tendons isolated from canine hearts. Records have been made during spontaneous activity and during electrical stimulation, and changes in electrical excitability and membrane resistance have been determined. The composition of the perfusing medium has been varied to change pH from the normal value of 7.2 to 7.8 or 6.7 either by increasing or decreasing the P_{CO_2} or the concentration of HCO_3^-. The effects of ouabain (0.125 mg./L.) have been studied at each pH in each perfusion medium. A concentration of ouabain which has no toxic effects at pH 7.2 causes marked deterioration of electrical activity if pH is increased or decreased within this range and also, at approximately normal pH, if P_{CO_2} or HCO_3^- is markedly changed. The changes in the transmembrane potentials include increased intrinsic rhythmicity, the appearance of multifocal pacemakers, a decrease in the magnitude of the resting potential and in the rate of rise and amplitude of the action potential and, terminally, a loss of excitability. The concentration of ouabain employed causes only a sustained positive inotropic effect on isolated canine ventricular muscle preparations, and thus is presumed to be comparable to concentrations employed in the clinic.

Four-year Evaluation of Surgical Correction of Mitral Regurgitation by the Open Technic

Earle B. Kay and H. A. Zimmerman, Cleveland, Ohio

Over 150 patients with mitral regurgitation have now had surgical correction by the technics possible by the open direct-vision approach. The technics employed are dependent upon the presenting pathologic factors. Approximately 30 per cent have had pure mitral regurgitation. The others have had combined mitral stenosis–mitral regurgitation. The underlying surgical principles have remained the same, but there have been a number of improvements and modifications of the technics to assure greater success. The operative mortality has been reduced to less than 10 per cent. A sufficient number of patients has now had surgical correction to allow an opinion as to indications and time of surgical intervention. The success of surgery has been so great that we now feel that surgical correction is indicated once the diagnosis of mitral regurgitation with altered hemodynamics is made, and it is not necessary to await evidence of failure or severe cardiomegaly.

Postoperative evaluation studies are performed approximately 1 year following surgical correction. Over 85 per cent of the patients have shown marked benefit. The factors contributing to lesser degrees of benefit have been analyzed.

Right Atrial Approach to the Surgical Correction of High Pressure Ventricular Septal Defects

Jerome H. Kay, Robert M. Anderson, William E. Bloomer, John E. Meihaus, Oscar Magidson, and Morse J. Shapiro, Los Angeles, Calif.

The mortality, throughout the country, in open heart surgery for patients with high pressure ventricular septal defects has been high. Our mortality in patients with low to moderate pressure ventricular septal defects is 1 out of 60 patients. However, until recently, our mortality in high pressure ventricular septal defects, in other words, those patients who have a pulmonary artery pressure of 70 per cent or higher than the systemic pressure, has been 7 out of 14 patients.

During the past year and a half, the authors have changed their surgical approach in the patients with high pressure ventricular defects. In these patients, the ventricular septal defect has been closed through the right atrium. The right ventricle is not opened, and, postoperatively these patients have done much better than the previous patients with a ventriculotomy. The mortality in the first 12 consecutive patients with high pressure ventricular septal defects operated upon through the right atrium has been zero. It has been felt that the reason for this marked difference is that with the increased pulmonary vascular resistance, a right ventricle with a large incision is unable to propel the blood into the pulmonary artery and the patient therefore goes into right-sided ventricular failure and dies. In those patients in whom the atrial approach has been used, it is felt that the right ventricle is spared and, therefore, it is able to overcome the pronounced pulmonary vascular resistance.

Systemic and Pulmonary Embolisms Before and After Mitral Commissurotomy

Frederick Kellogg, Long Beach, Calif., Chi Long Liu, Torrance, Calif., I. William Fishman, Long Beach, Calif., and Roger Larson, Torrance, Calif.

It has been stated that systemic embolism is an indication for mitral commissurotomy. This investigation was initiated by the frequent occurrence of systemic and pulmonary embolic episodes in mitral patients at surgery and in the follow-up period. It includes 149 patients. The average postoperative follow-up was over 3 years.

There were 13, or 8.7 per cent, surgical deaths. Four of the 13 deaths were due to cerebral embolizations. Five additional patients had systemic embolization at surgery but survived. There were 11, or 8.1 per cent, late deaths in 136 patients.

Prior to surgery, 42 of the 149 patients, or 28 per cent, had systemic emboli, 69 per cent of whom had atrial fibrillation. Postoperatively, 17 of the 136 surviving patients, or 12.5 per cent, had evidence of late systemic embolism, 76 per cent of whom had atrial fibrillation. There were at least 21 episodes of systemic embolism. Thus, the incidence of late systemic emboli was 0.051 per cent per patient year. Twelve of these 17 patients had systemic embolism after surgery for the first time. Including those patients with emboli at surgery, a total of 26 patients had systemic embolism. This figure is significantly high. There were 10 patients who had pulmonary embolism before surgery and 10 in the follow-up period.

Systemic embolization as an indication for mitral commissurotomy, regardless of the patient's clinical symptoms, should be carefully reconsidered.

Effect of Cigarette Smoking and Nicotine Administration on Serum Free Fatty Acids

Alfred Kershbaum, Samuel Bellet, Edward R. Dickstein, Leonard J. Feinberg, and Paolo Rossi, Philadelphia, Pa.

The response of serum free fatty acids (FFA) to cigarette smoking was studied in 17 subjects. Two cigarettes were smoked in a 10-minute period and the serum FFA concentration was determined before and after smoking and at subsequent 10-minute intervals. In all subjects, the FFA levels rose at the end of the smoking period, and the maximal elevation usually occurred 10 minutes later. Twenty and 40 minutes after smoking, the FFA were still above the presmoking level in most instances. The maximal rise in FFA varied from 98 to 590 μEq./L., with a mean increment of 291 μEq./L. There was essentially no change in the serum total cholesterol and triglycerides in these experiments. In a control group who did no smoking, there was an average increase in FFA of 4 μEq./L. over a 20-minute period. In order to simulate "chain-smoking," another group of 5 subjects smoked 6 cigarettes over a 40-minute period. All of these subjects showed a rise in FFA which was sustained throughout a total interval of 60 minutes. In animal studies, nicotine was administered by continuous intravenous infusion at a rate of 20 γ/Kg./min. over a 20-minute period. In 13 of 15 observations there was a mean maximal elevation of FFA of 166 μEq./L., which usually occurred 10 minutes after the start of infusion. The observations made in these studies indicate that cigarette smoking and nicotine administration are followed by a mobilization of FFA. These findings suggest the possibility that a repeated rise in FFA could be related to a disturbance in other serum lipids.

Combined Transthoracic Left and Percutaneous Right Heart Catheterization: Its Risk and Value in Evaluation of the Lesions of the Mitral and Aortic Valves

Paul Kezdi, Chicago, Ill.

Combined left and right heart catheterizations were performed in 150 patients with lesions of the left side of the heart by transthoracic left atrial puncture and simultaneous percutaneous catheterization of the right heart using a polyethylene catheter. The latter required no fluoroscopy. The pulmonary artery could be entered by oscilloscopic monitoring of the pressure in 90 per cent of the cases, the right ventricle in 98 per cent. Cardiac output and pressure gradients were determined simultaneously and valvular areas were calculated.

Characteristic hemodynamic changes and relation of pressure and flow to valve area in the different valvular lesions were studied. The largest single group studied had pure mitral stenosis. The rest had mitral stenosis and regurgitation, aortic stenosis, combined aortic and mitral lesion, and nonvalvular heart condition, in decreasing order. Valuable information was obtained supplementing the clinical findings and aiding the clinician in his decision in recommending surgical treatment. In a significant number of instances (10 per cent), the findings were contrary to the clinical impression. In combined valvular lesions, the predominant lesion could be evaluated with great accuracy.

Mitral regurgitation was evaluated by injection of Cardio-green into the left ventricle and withdrawal of blood from the left atrium through a second needle and a Gilford densitometer, using the pooled sample technic for obtaining mean concentration. Regurgitant flow was calculated from the dye curve.

Serum Lipoprotein Alterations Induced by an Orally Active Heparinoid, Sulfopolyglucin

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Oral administration to man and animals of sulfopolyglucin (SPG), a characterized sulfated polysaccharide, is followed by appearance of a lipoprotein lipase in blood plasma. Gastrointestinal absorption is enhanced by concomitant ingestion of sodium "Versenate" (V). A mixture of SPG and V (4:1) was given to 28 human subjects in daily doses of 2 to 6 Gm. (of SPG) for periods of 1 to 6½ weeks. Sf° 12-400 serum lipoprotein concentrations, studied in 26 subjects, decreased impressively in 15, in many of whom pretreatment values had been relatively high. Dramatic lowering was observed in 4 of 6 subjects given single doses of 2 Gm. daily: pretreatment values—293, 211, 129, 112 mg. per cent; after 2 weeks of treatment—136, 156, 94, ?; after 4 weeks of treatment—39, 39, 53, 36 mg. per cent, respectively. The daily 2 Gm. dose was still being well tolerated by all 6 subjects after 6 weeks of treatment. In other subjects, serum lipoprotein concentrations, depressed in the course of 6 weeks of treatment with daily doses up to 6 Gm., were still below pretreatment values on the fiftieth day after discontinuance of treatment. Lee-White whole blood coagulation times were not affected.

Changes in Mortality Rates of Surgically and Medically Treated Patients with Hypertensive Disease over a Ten-year Period

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The impact of drugs on mortality rate in hypertensive disease was observed by comparing the 5-year mortality rates of medically and surgically treated patients in the pre- and post-drug era. The material consisted of 2,822 patients seen for the first time in a period from 1944 through 1954. The mortality rates were calculated for groups divided according to the Smithwick classification, sex, and form of treatment. The results indicate that the over-all mortality in the medically treated group has become more favorable in the post-drug era, falling from 53 to 27 per cent. The surgically treated patients, in comparison, showed an increase from 18 to 24 per cent. The improvement in medical mortality was seen in all groups, but was most marked in groups I and II. The increase in mortality in surgically treated cases was seen mostly in group III. However, a lower mortality in surgically treated patients compared to medically treated patients continued to be highly significant in group III particularly. These differences could not be attributed to composition of group in regard to age, sex, or degree of involvement of the cardiovascular system at the original examination. It seems reasonable, therefore, to attribute the decrease in mortality of medically treated patients to effectiveness of drugs. The increase in mortality of surgical patients, however, being unexplained by any of the above-mentioned parameters, or operative mortality, must be explained by other subtle factors such as screening out of "responsive" patients by drug treatment, or longer interval between onset and operation due to trial and failure of drugs.

Retrograde Conduction to the Atria in Ventricular Tachycardia Complicating the Differentiation from Supraventricular Tachycardia with Aberrant Ventricular Conduction

Albert D. Kistin, Beckley, W. Va.

This study demonstrates that retrograde conduction to the atria in ventricular tachycardia is common, and that this complicates the electrocardiographic differentiation from supraventricular tachycardia with aberrant ventricular conduction. It has previously been demonstrated that retrograde conduction from isolated ventricular premature systoles is common in man, and the author's further experience confirms this. Runs of ventricular tachycardia, at least 5 ventricular ectopic systoles in succession, were recorded by means of simultaneous esophageal and standard leads in 20 cases. The onset of the run of tachycardia was recorded in each case so that the origin of the tachycardia is established. Retrograde 1-to-1 conduction occurred in 8 cases. Retrograde conduction with varying degrees of ventriculoatrial block occurred in 4 cases. An independent atrial rhythm, the usually described mechanism in ventricular tachycardia, occurred in only 8 of the cases. It has been claimed that supraventricular tachycardia with aberrant ventricular conduction may be identified in esophageal leads by finding a 1-to-1 P-to-QRS relationship. The present study does not support this claim; in the presence of a 1-to-1 P-to-QRS relationship, identification of the origin of the tachycardia may be possible only if the tracings show the onset of runs of the tachycardia.

Analysis of the Factors Affecting the "Resting" Free Fatty Acid Level in Normal Man

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Plasma free fatty acids (FFA) have been shown to provide a potentially significant source of meta-

bolic substrate for the myocardium in man. Experiments providing these data utilize the technics of arteriovenous differences of FFA across the heart and depend in large part on the serum level during the "resting" state. An analysis has been made of the factors which influence and modulate the "resting" FFA level in man and, therefore, in part, the availability of this substrate.

Results of the studies in 69 normal subjects observed in the laboratory in a controlled setting may be summarized as follows: (1) the fasting plasma FFA level in nonobese as well as obese individuals is linearly related to body weight when the effect of fasting is held constant ($p < 0.05$); (2) the duration of fasting is of itself a direct determinant of the "resting" level ($p < 0.01$); (3) the duration of fasting influences the direction and magnitude of the change in FFA level following a standardized arousing stimulus ($p < 0.01$).

These variables have been further assessed in a review of the responses to a specific hormonal stimulus (norepinephrine) in 43 subjects. The marked variability of these curves may be dependent, in part, on these factors.

These studies provide evidence that the relative availability of an important substrate of the myocardium during the "resting" state is significantly and interrelatedly modified by body size, fasting time, and arousal. These factors, therefore, must be viewed as prior considerations in designing studies of FFA transport and extraction in man.

Ability of Magnesium to Substitute for Calcium in the Electrocardiogram

Robert M. Kohn, Buffalo, N. Y.

When the isolated rabbit heart is perfused with Chenoweth's solution containing EDTA in critical concentrations of 0.5 mg. per cent, contraction ceases but the electrocardiogram continues and exhibits a prolonged S-T interval. This effect is typical of calcium deficiency. When an excess of EDTA is added, marked electrical instability is produced, with ventricular fibrillation followed rapidly by irreversible standstill. These effects suggest that other cations, in addition to calcium and magnesium, have been bound. When the Chenoweth's solution is made up with calcium excluded and with magnesium substituted for the calcium on a molar basis, the mechanical beat will cease, but there will be no significant change in the electrical activity and no electrocardiographic signs of calcium deficiency. This suggests that magnesium is capable of substituting for calcium in the membrane effect responsible for the electrocardiogram. However, it is not capable of substituting for calcium in the contractile process.

Biochemical Studies in Full-blooded Navajo Indians: II. Lipids and Lipoproteins

Robert J. Kositchek, Moses Wurm, and Reuben Straus, Burbank, Calif.

Epidemiologic studies of primitive ethnic groups have implied the presence of some genetically determined protective mechanisms, among other factors, to account for the low incidence of coronary heart disease. This has been the case in the Navajo Indian, presumably subsisting on a "typical American diet." Since we have shown that elevated globulins in the Navajo Indian are not genetically determined and probably not related to the low incidence of coronary heart disease, further studies were made of the blood lipids.

Random early morning blood samples were collected in the interior of the reservation from 30 full-blooded Indians having a mean age of 48 years. Standard lipid analyses, including paper lipoprotein electrophoresis, revealed strikingly low individual and mean values. With the exception of 3 elevated values found in lipemic specimens knowingly taken postprandially, the beta/alpha lipoprotein ratios ranged between 0.38 and 2.33 (mean 1.49) which, as an index of atherogenesis, correlates with the general absence of coronary heart disease.

Statistical comparison of these data with those in 3 control populations ("normals," patients with manifest atherosclerosis, and tuberculous patients) showed significantly lower cholesterol concentrations, C/P ratios and beta/alpha ratios.

Preliminary observations of dietary habits revealed that although the Navajo Indian may consume foods rich in fat, the quantity is markedly restricted by availability and modified by unique preferences so that it cannot be considered a "typical American diet." It is concluded that the general absence of coronary heart disease in this ethnic group is a product of their low caloric diet, together with an unimpaired lipid metabolism, and that this is reflected by a low beta/alpha lipoprotein ratio.

Long-term Anticoagulant Therapy after Acute Myocardial Infarction

Paul B. Kuhn, Chicago, Ill., Albert L. Van Ness, Bloomington, Ill., Richard J. Jones, and Barbara S. Helmstetter, Chicago, Ill.

In a 10-year experience, 736 consecutive cases of acute myocardial infarction were treated at the University of Chicago Clinics. Of the 601 patients who survived for 6 weeks, 583 were followed for 2 years or until death. These patients were divided into 3 groups: 166 patients who were treated with anticoagulants (group I), 270 patients who served

as controls for the entire observation period (group II) and 147 patients who were treated during part of the 2-year period (group III).

Twenty-one patients in group I died within 2 years (13 per cent), which represents a significantly ($p < 0.01$) lower mortality than the 71 deaths in group II (26 per cent). Most of the deaths in both groups were due to recurrent myocardial infarction.

Since group III consisted mainly of treated patients who stopped therapy because they were asymptomatic and control patients who were started on therapy because of a recurrent infarction, exclusion of these patients from groups I and II caused an underestimation of the differences between the latter 2 groups. When these patients were included in the calculations, 313 patients were treated with anticoagulants for 1.37 years per patient and 417 controls were observed for 1.42 years per patient. There were 24 deaths (7.7 per cent) and 23 recurrences (7.3 per cent) in the treated patients compared to 85 deaths (20.4 per cent) and 66 recurrences (15.8 per cent) in the controls ($p < 0.01$).

From these data it is concluded that the administration of long-term anticoagulant therapy after a myocardial infarction prolongs life and helps prevent recurrent myocardial infarction for at least 2 years.

Fall of Serum Potassium Concentration and Appearance of Cardiac Arrhythmias during Infusion of Potassium with Glucose in Patients wth Hypopotassemia

Arthur S. Kunin, Borys Surawicz, and Ethan A. Sims, Burlington, Vt.

This study was prompted by the observation of 2 hypopotassemic patients treated with conventional amounts of KCl and glucose. During intravenous infusion, 1 patient developed ventricular extrasystoles and ventricular tachycardia, and the other, ventricular extrasystoles, ventricular tachycardia and lethal ventricular fibrillation. It was suspected that cellular uptake of potassium with glucose lowered serum potassium concentration, altered potassium gradient across myocardial cell membranes, and precipitated arrhythmia.

KCl was given intravenously at a constant rate under electrocardiographic control in 15 patients with potassium depletion and 2 normal individuals. In 8 patients, serum K was below 3.5 mEq./L. The rates of potassium infusion per hour were: 40 mEq. in 10 per cent glucose in 6, 40 mEq. in 5 per cent glucose in 3, and 20 mEq. in 5 per cent glucose in 8 persons. Serum K concentration was determined every 15 minutes.

Results were similar in all 3 groups. After 15 minutes, serum K concentrations were lower than the control concentration in 9, after 30 minutes in 8, after 45 minutes in 5, after 60 minutes in 4, and after 75 minutes in 3 persons. The largest fall was 1.3 mEq./L.

Four of 8 patients receiving maintenance doses of digitalis developed the following transient changes in rhythm: atrial extrasystoles, appearance and increase of ventricular extrasystoles, and a change from 2:1 to 1:1 block in atrial tachycardia.

It is concluded that in the face of hypopotassemia and treatment with digitalis, intravenous administration of potassium with 5 per cent and 10 per cent glucose may be unsafe.

Coronary Sinus Method as an Adequate Measure of Left Ventricular Coronary Flow and Metabolism

Robert Lafontant, Harold Feinberg, and Louis N. Katz, Chicago, Ill.

Information about cardiac metabolism and coronary flow has been obtained by extrapolating coronary sinus catheterization data. Coronary sinus drainage has been considered representative of left ventricular coronary supply. The assumptions involved have not been verified. A new preparation permitted investigation of the distribution of flow and metabolism in the myocardial areas drained by the coronary sinus and the other coronary venous channels. The parameters of these two beds were measured simultaneously under controlled variations in heart rate, cardiac output, and independent modification of the right and left ventricular work loads. It was noted that:

1. Coronary sinus flow averaged 57 per cent of the total; however, some variations occurred in the same experimental dog and considerably more between animals (47 to 67 per cent).

2. The O_2 content in the coronary sinus was not representative of the mixed coronary venous drainage.

3. Alterations of the work of either ventricle resulted in unequal blood flow, arteriovenous O_2 difference, and O_2 consumption changes in the two drainage beds.

4. Total O_2 consumption, even when the right ventricle was doing little work, correlated well with our cardiac effort index (heart rate times mean blood pressure); however, extrapolation of total cardiac O_2 consumption and coronary flow from coronary sinus blood determination alone did not correlate nearly so well.

Thus, if the amount and character of the drainage by the other coronary venous channels are not taken into consideration, serious misinterpretations of the total coronary flow and myocardial oxygen consumption may result. Furthermore, the implications of the coronary flow through the left ven-

tricle and its O_2 utilization are not necessarily valid if based on the coronary sinus drainage alone.

Mechanism of Early and Late Ventricular Captures in Advanced A-V Block within Complete A-V Dissociation: Interplay of Unidirectional Block, Concealed Conduction, and Supernormal Phase of Conduction in the A-V Junction

Richard Langendorf and Alfred Pick, Chicago, Ill.

Concealed and supernormal conduction are intimately related phenomena since concealed conduction may occur as a result or, occasionally, as the only manifestation of a supernormal phase, and contrariwise a supernormal phase may develop in the wake of concealed conduction. If a region of unidirectional block is present in the A-V junction that permits retrograde impulses (of the subsidiary pacemaker) to traverse a region of forward block, then (concealed) retrograde conduction across the region of unidirectional block may render the depressed region responsive for subsequent appropriately timed forward (sinus) impulses by temporarily changing the region of forward block to one of supernormal conductivity (early ventricular capture). Once forward conduction across the region of unidirectional block is initiated in this way, it may continue as long as the atrial rate is such that each impulse falls into the supernormal phase after the preceding one.

On occasion a forward impulse that passes the region of unidirectional block as a result of a supernormal phase of conduction may be blocked beyond that region and yet be responsible for complete passage of the next forward impulse. Thus, concealed retrograde conduction across a region of unidirectional block may induce concealed forward conduction across the region which in turn is followed by full forward conduction during the supernormal phase—a hitherto undescribed manifestation of supernormal phase responsible for ventricular captures occurring late in the ventricular cycle.

Hemodynamic Correlation with the Electrocardiographic Pattern of Left Ventricular Hyportrophy–"Diastolic Overloading"

Jerry J. Lasser and Richard P. Lasser, New York, N. Y.

Forty-two cases of isolated ventricular septal defect were used to examine the concept of "diastolic overloading" (DO) in left ventricular hypertrophy (LVH) from the standpoint of electrocardiographic, hemodynamic, and roentgenographic findings.

Each case read as LVH–DO had the characteristic pattern in V_6 of prominent Q wave, tall R wave with delayed intrinsicoid deflection, and tall peaked T wave. R-wave amplitude was required to exceed the normal range for age; Q and T-wave amplitudes had to be above the seventy-fifth percentile of normal range. Complete cardiac catheterization was performed in each case including either pulmonary capillary wedge, left atrial, or end-diastolic left ventricular pressure and calculation of shunt-systemic flow ratios. Cases with systolic gradients across the pulmonic valve greater than 15 mm. Hg were excluded.

Electrocardiograms were classified into 5 groups: normal limits 22, isolated LVH–DO 7, LVH–DO plus RVH 4, isolated RVH 7, and combined hypertrophy without evidence of LVH–DO2.

There were no differences in hemodynamic data between the group of isolated LVH–DO cases and patients with normal electrocardiograms. Both groups showed normal or slightly elevated pulmonary artery pressures and small to moderate left-to-right shunts. Pulmonary capillary wedge pressures were normal. Heart size, pulmonary vascular density, and left ventricular contour estimated from teleoroentgenograms showed no significant differences.

The group of LVH–DO plus RVH showed moderately elevated pulmonary artery pressures and moderate to large left-to-right shunts. Whenever right ventricular pressure exceeded 60 mm. Hg, the LVH–DO pattern did not appear.

Mechanism of Action of Sodium on Arterial Pressure

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An osmoreceptor circulatory reflex in dogs within the distribution of the femoral and brachial arteries can be stimulated by changes in tonicity of arterial perfusate and is capable of provoking a generalized sympathetic discharge. Thus, rapid intra-arterial injection of 2 to 80 cc. of 1.4 to 10 × hyperosmotic saline, dextrose, or urea in 54 dogs provoked arterial hypertension, tachycardia, and venoconstriction beginning 6 to 10 seconds after onset of injection and lasting 2 to 30 minutes. Magnitude of response was related to the degree of hypertonicity. These effects were not observed with intravenous hypertonic solutions or intra-arterial isotonic solutions. Intra-arterial hypotonic solutions produced slight hypotension. Temperature and pH of injectate, changes in blood volume, local arterial distention, and local vasomotor adjustments were excluded as factors.

The afferent arc of the reflex was relayed via somatic nerves without traversing the sympathetic

chain. Medullopontine transection did not alter the response, thus excluding participation of cortical and thalamic synapses.

Suggestive evidence that the reflex might be operative under physiologic conditions was obtained in 12 dogs by the elevation of arterial pressure of 25 to 40/15 to 20 mm. Hg which accompanied constant femoral intra-arterial infusion of hypertonic saline at a rate calculated to raise local arterial sodium concentration about 15 mEq./L. without appreciably elevating the sodium concentration or volume of the general circulation. Furthermore, reactivity was enhanced or depressed by an increase or decrease in the over-all serum sodium concentration.

These findings suggest that a sodium-sensitive osmoreceptor reflex may be a factor in hypertension.

Cyclic Reutilization of Cholesterol in Atherosclerotic Lesions

Abel Lazzarini, Jr., and Jere W. Lord, Jr., New York, N. Y.*

Endothelial cells obtained from the intima of short-term organ cultures of the aorta and coronary vessels of patients with severe atherosclerosis were maintained in media containing aqueous microemulsions of C^{14}-cholesterol. After incubation the cells were rinsed in a balanced salt solution and transferred to a cholesterol-free medium.

It was observed that those cells which had high concentrations of intracellular cholesterol did not return to their initial state but degenerated, and their protein-bound cholesterol was immediately incorporated by surrounding cells of the same type. This cyclic reutilization would then continue until all endothelial cells were destroyed unless the process was inhibited by the addition of heparin or unsaturated acids to the medium.

These results suggest that cholesterol reutilization may play a role in atherosclerosis which could explain the clinical findings of atherosclerotic patients with normal cholesterolemia since atherogenesis could continue independent of blood cholesterol levels once the initial arterial lesion had been produced.

Cardiac Lesions in Rheumatoid Disease

Wallace B. Lebowitz and Bruce Cruickshank, Boston, Mass.

The uncertain etiology of cardiac lesions in patients with rheumatoid disease prompted a study of 61 consecutive cases of *peripheral* rheumatoid arthritis autopsied at the Boston City Hospital. In a control group of 122 cases matched for age and sex, rheumatic heart disease was encountered in 11, calcific aortic stenosis in one, degenerative lesions at the valve bases and rings in 7, and nonspecific lesions in 6 (5 per cent).

In the series population rheumatoid granulomas were observed in 2 hearts, rheumatic heart disease in 5, calcific aortic stenosis in 4, and degenerative lesions at the valve bases and rings in 13. Coronary atherosclerosis, however, was present with equal incidence and severity.

Lesions not clearly related to other etiologic forms of cardiac disease were present in 36 rheumatoid patients (60 per cent). These included pericardial lesions in 13, myocarditis in 11, arteritis in 11, and chronic valvulitis in 3, while 15 exhibited thickening and fibrosis of the valve bases and rings which histologically resembled healed rheumatic endocarditis. However, the absence of other criteria for rheumatic heart disease, as defined by Gross and others, and the presence of extracardiac visceral manifestations of rheumatoid disease in most patients strongly suggested that these lesions were part of the rheumatoid process.

Thus, rheumatoid disease appeared to be associated with distinct cardiac lesions. Furthermore, pre-existing rheumatoid disease may have been responsible for the increased incidence of calcific aortic stenosis and degenerative lesions at the valve bases and rings, sites of predilection for rheumatoid granulomas.

Pre- and Postoperative Assessment of Aortic Stenosis

Martin Lees, Anna J. Hauck, Abraham M. Rudolph, Alexander S. Nadas, and Robert E. Gross, Boston, Mass.*

Forty-two cases of congenital aortic stenosis surgically treated with cardiopulmonary bypass have been followed for periods of 6 to 38 months postoperatively.

Valvular stenosis was present in 26 and subvalvular in 11. Three children had hypoplasia of the aortic valve and ascending aorta, and 2 additional cases had associated endocardial disease. Six patients succumbed at surgery; 4 had complicated lesions, and 2 were infants under 2 months of age. Postoperative left heart catheterization in 7 patients revealed marked reduction of the gradient in 4.

Serial electrocardiograms showed appreciable improvement in 13 of 16 patients with valvular stenosis with adequate follow-up; in 2 of the remaining 3 the gradient across the aortic valve was shown to be unchanged.

None of the 11 patients with subvalvular stenosis showed electrocardiographic improvement in spite of complete abolition of the gradient in at least 2 instances.

Postoperative electrocardiographic improvement was independent of age or the duration of preoperative electrocardiographic changes. Favorin

the diagnosis of subvalvular stenosis was the presence of a protodiastolic blow (10 of 11 cases) and the absence of an aortic ejection click (all cases).

Left heart catheterization adequate withdrawal tracings were obtained in 5 of the patients with subaortic stenosis, and in 4 of these the subvalvular chamber was demonstrated.

Being aware of the unreliability of the peripheral arterial pressure tracing in the estimation of the severity of the stenosis, we studied the central arterial pressure pulses and found them to be equally unreliable.

Renal Ultradialysis as an Adjunct in the Surgical Treatment of Heart Disease

William M. Lemmon, Charles P. Bailey, Teruo Hirose, and Robert A. O'Connor, New York, N. Y.

A problem all too frequently faced by the cardiac surgical team is the patient with a potentially remediable lesion in intractable congestive heart failure. It occurred to us that application of the artificial kidney in such instances might possibly succeed where all other forms of medical therapy had failed to "dry out" the patient.

Others have dialyzed patients in congestive heart failure, but none has reported following through with surgical correction of the underlying lesion. Such cases carry a high risk for dialysis and heart surgery, but the risks must be accepted. Without the 2-fold attack on the dual problem the mortality with medical therapy is practically 100 per cent.

Once the patient is relieved of congestive heart failure, a proper work-up can be performed, including diagnostic tests and evaluation for operation. After the program is inaugurated, the regime must be pursued quickly and vigorously, including operative intervention with correction of the lesion. Otherwise the patient will relapse into intractable failure.

Dialysis may have to be repeated on one or more occasions. Patients refractory to all diuretic measures have been found to have a profuse diuresis subsequent to successful renal dialysis. There are several possible explanations for this phenomenon. Each dialysis, using a hypertonic bath solution, is run with full laboratory control and continued to the time and physiologic limit of the patient.

This preliminary report summarizes our initial experience with the artificial kidney, employing the ultrafiltrate principle, in patients with intractable heart failure.

Histopathologic Study of the Atrioventricular Communications in Two Hearts with the Wolff-Parkinson-White Syndrome

Maurice Lev, Chicago, Ill., Rexford Kennamer, Myron Prinzmetal, Los Angeles, Calif., and Quintiliano H. De Mesquita, Sao Paulo, Brazil

Two hearts of patients with the Wolff-Parkinson-White syndrome associated with possible Chagas disease were studied histopathologically. One patient had complete right bundle-branch block in addition. The study was done by serial sectioning of the entire A-V junction at the mitral and tricuspid orifices and the approaches to the A-V node, the A-V node and bundle, and the bundle branches. The atria and ventricles were also completely sectioned, and the S-A node was studied in one case.

Both hearts were the seat of chronic myocarditis, which in one heart was positively and in the other possibly Chagasic in type. Accessory atrioventricular communications between the right atrium and ventricle were found in one heart and not in the other. Inflammatory changes involved the approaches to the A-V node in both hearts, the A-V node in one heart, and the bundle of His and both bundle branches in both hearts. There was elastosis of the second A-V node. The right bundle branch was completely obliterated in the case with the complete right bundle-branch block.

The anatomic literature on the Wolff-Parkinson-White syndrome together with our material reveal that this syndrome can occur without A-V node bypass, and accessory communications have been found without the syndrome being present. It is therefore possible either that A-V node bypass is not the mechanism of this syndrome or that there are 2 anatomic substrates for this anomaly—one with and one without accessory A-V communications. Where no communications are found, accelerated conduction may be invoked as the mechanism for its production.

Pathologic Methods for the Study of the Entire Congenitally Malformed Heart for Electrocardiographic and Physiologic Correlation

Maurice Lev and Ursula F. Rowlatt, Chicago, Ill.

An attempt has been made to evolve semiquantitative pathologic methods of study in congenital heart disease which can be used for electrocardiographic and physiologic correlation so as to reinforce qualitative methods. Findings were based on a simultaneous study of 80 normal hearts from birth to 15 years of age, all references in the pathologic heart being compared to the normal heart of the same age.

The heart was studied in stages. The external examination covered shape and size of the heart, the position of the anterior descending coronary artery, the composition of the apex, the position of the atrial appendages, and the position of the arterial trunks. This made possible the prediction of the internal anatomy in many cases and hence was useful to the surgeon. The internal examina-

tion, in addition to the usual morphologic phenomena, included the endocardial pattern and valves, thickness of walls and various internal wall measurements, and the weights of the parietal ventricular walls to yield volume and thickness indices from which statements of hypertrophy and dilatation were made. The results of the study up to this point may prove sufficient for correlation with catheterization data.

The heart was then completely sectioned for microscopic examination. This included skip-serial sectioning of the S-A and A-V nodes and their approaches, the A-V bundle and bundle branches, and complete sampling of the atria, ventricles, and septa, which yielded from 250 to 500 sections. This entire study was necessary for electrocardiographic correlation.

From this study, the concepts of pressure and volume hypertrophy, dilatation without failure, and hemodynamic changes of endocardium and valves were developed.

Inefficient Myocardial Oxygen Utilization in Congestive Failure: Consequence of Cardiac Dilatation

Herbert J. Levine, William A. Neill, Richard J. Wagman, Joseph V. Messer, and Richard Gorlin, Boston, Mass.

Thirteen patients in congestive failure and 17 controls were studied by coronary sinus catheterization at rest and during exercise. Myocardial oxygen consumption (qO_2) and left ventricular dynamics were determined in all. At rest left ventricular qO_2 per unit weight in the congestive failure group bore the same relationship to tension-time index (TTI) as the controls. Resting inefficiency in congestive failure became apparent only when the *total* left ventricular qO_2 was related to left ventricular work (or TTI). Thus, in 7 necropsied failure cases, total left ventricular qO_2 was more than 3 times the controls. This left ventricular contribution to the metabolic rate was reflected in a 19 per cent increase in total body qO_2 in the congestive failure group.

With exercise left ventricular qO_2/unit weight rose significantly more in the failure group than in the controls for a given increment in left ventricular work or TTI. Despite large rises in left ventricular filling pressure, stroke work failed to increase. Mechanical efficiency, which rose 44 per cent during effort in the controls, was unchanged in the congestive failure group. While this inefficiency was related partly to the tachycrotic response of the failing heart, the left ventricular qO_2 *per heart beat* rose abnormally. This is explained by La Place's Law which relates fiber tension to the radius of the ventricular chamber. Unlike the normal left ventricle, the dilated failed heart, unable to decrease its internal surface area sufficiently during systole, may be forced to exert progressively greater tension while shortening, thus limiting its ability to contract while increasing its O_2 need. The failed ventricle, therefore, while structurally suited for high flow work, paradoxically performs costly pressure work. The data support the Starling-Frank hypothesis on congestive failure only so far as energy expenditure is concerned, excluding work developed.

Measurement of Mitral Regurgitant Flow from Indicator-Dilution Curves After Injection into the Left Ventricle

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In previous reports we suggested that after injection of indicator into the left ventricle, mitral regurgitant flow (Q_R) was calculable from systemic flow (Q_S) and the areas (A_{LA} and A) under initial left atrial and arterial dilution curves, as $Q_S/[(A/A_{LA})-1]$. The requirements were as follows: Ventricular mixing had to be complete in diastole and atrial mixing in systole, measured atrial concentrations had to represent equilibration in the total stroke volume, and the initial atrial curve had to reflect only regurgitation.

Twenty-five studies were performed in 16 patients. Operative findings (10) and clinical and physiologic assessment (6) permitted classification of regurgitation as negligible (4), mild to moderate (6), and moderately severe to severe (6). Mean Q_R, as a percentage of total left ventricular output (Q_T), was 6 per cent (0 to 11 per cent), 21 per cent (8 to 39 per cent), and 58 per cent (27 to 82 per cent), respectively. Thus, Q_R reflected severity of regurgitation. However, differences between duplicate determinations (7 patients) were large (mean 18 per cent and S.E. 6 per cent of Q_T), and in 2 patients impossible values were calculated on one of 2 measurements.

Moreover, in all studies violation of one or more of the requirements was evident. In most the sampling system modified the atrial curve which therefore misrepresented the concentrations obtaining during ventricular filling. Five patients demonstrated incomplete mixing. In one patient regurgitation was overestimated because early recirculation from demonstrated bronchopulmonary anastomoses coincided with regurgitant flow. Similar overestimation could be inferred in another. In 2 the primary atrial curve merged with general recirculation.

Thus, this theoretically ideal method, although useful, is subject to profound error, some of which is not amenable to correction by multiple measurements and technical refinements.

Total Prosthetic Replacement of the Mitral Valve—An Experimental Study

Bernard S. Levowitz, John B. Lovette, Mario Lecce, Ram S. Ratan, George J. Magovern, and Edward M. Kent, Pittsburgh, Pa.

This presentation deals with the prosthetic replacement of the mitral and tricuspid valves in 72 animals. The experiments were conducted under total cardiopulmonary bypass and mild hypothermia.

The initial phase consisted of placement of rings of Dacron, silastic, dacron, methyl methacrylate, and silk in juxtaposition to the mitral annulus without disturbing valve function. Eighty per cent of the animals in this group died of mitral stenosis due to exuberant thrombus at the annulus in addition to extensive peripheral embolization. Incorporating these materials in homologous artery or vein appeared to limit the propensity for thrombus formation.

In 11 animals the tricuspid valve was replaced with a silastic tricuspid prosthesis. One animal survived for 7 days and succumbed to massive thrombosis at the valve orifice. The remaining dogs developed lethal conduction defects and died in the immediate postoperative period.

The mitral valve was replaced in 40 animals. Bicuspid, tricuspid, quadricuspid, and flipper designs were employed. Several types of materials were used, including silastic, lucite, Teflon, and arterial homograft. Although most valves functioned in vitro, in vivo performances were disappointing. Thrombosis with valvular obstruction was the chief cause of death after 5 to 7 days survival. Thirty-day survival was obtained with homologous aortic valve, reversed and placed in the mitral ring. Most encouraging results are currently being achieved with an open, nonrigid, quadricuspid valve lying entirely within the left ventricule. Thrombosis at the point of fixation to the annulus appears to be prevented by covering this area with homologous graft material.

Effects of Temperature on Membrane Potentials from Rabbit S-A Node in Vitro

Joseph V. Levy,† San Mateo, Calif., and Theodore C. West, Seattle, Wash.

The effects of temperature changes on membrane action potentials from rabbit S-A node have been studied using the microelectrode technic. Increasing the temperature produced an increase in the rate of slow diastolic depolarization (RSDD) concomitant with an increase in action potential discharge rate. Lowering the temperature slowed the RSDD with a concomitant decrease in action potential discharge rate. The degree of change in the RSDD was found to vary with different pacemaker cell types. However, for any given type the action potential discharge rate ("sinus rate") was directly proportional to the RSDD and temperature over the ranges studied (22 to 41 C.). The mean temperature coefficient (Q 10) for the RSDD was 4.15 for the three cell types studied. For cells in the center of the S-A node ("true pacemakers"), the mean Q 10 for the RSDD was 5.89 (range 3.81 to 9.0). Cells near the border of the S-A ring bundle (which were characterized by the slowest RSDD) had a mean Q 10 of 3.10 (2.60 to 5.32). The mean Q 10 for the RSDD of pacemaker cells from the septal margin of the S-A ring bundle was 3.05 (2.41 to 3.88). The mean Q 10 for the frequency of action potential discharge of all three cell types was 2.54 (2.02 to 3.08). Thus, pacemaker cell activity may be differentiated not only by anatomic localization but also by differences in responses of the RSDD to temperature changes. True pacemaker cells show the greatest reactivity to temperature changes.

Fibrinolytic Activity of Arterial Tissues

Jack Lieberman and Frederick Kellogg, Long Beach, Calif.

A study of the plasminogen activator within the walls of arteries was undertaken to investigate the possibility that an intrinsic deficiency in fibrinolysis may predispose to intravascular fibrin deposition as the initial stage of atherosclerosis. Plasminogen activator was assayed by means of a fibrin-plate technic. Activity was expressed as the product of 2 perpendicular diameters through the area of lysis which results from the application of a 5-mm. disc of arterial tissue to the fibrin plate for 24 hours at 37 C.

Plasminogen-activator activity was found localized in the adventitial layer in almost all vessels studied. Enzyme activity appeared incapable of penetrating the intact intima, although minimal activity was detected within areas of erosion accompanying moderate to marked atherosclerosis. In a study of fetal aortas a maturation delay in the appearance of the enzyme was evident so that fetuses less than 2,000 Gm. in weight lacked activity. In adult males activity of the aorta appeared fairly constant in all age groups, although somewhat higher levels were observed in those over 60. Females differed in that activity was higher at ages under 60 but dropped to comparable male levels at higher ages.

Variation in the level of enzyme activity was also observed between the different arteries studied. The basilar artery showed the lowest activity (242 $\pm$ 282 units, n = 26) < pulmonary artery (316 $\pm$ 221, n = 29) < renal artery (638 $\pm$ 276, n = 23)

= abdominal aorta (716 ± 383, n = 130) = arch of aorta (745 ± 448, n = 142) = coronary artery (746 ± 524, n = 106). A difference between the coronary arteries of males and females also was seen: males—642 ± 467 units, n = 53; females—836 ± 557 units, n = 53. No correlation was observed between the presence of atherosclerosis within the aorta or coronary arteries and the level of enzyme activity.

From these data it would appear difficult to assign a role for the pathogenesis of atherosclerosis to the plasminogen activator of arterial tissues other than that related to its customary absence from the vascular intima. The differences in enzyme activity observed between males and females are of interest, but their importance cannot be assessed at this time.

Thromboembolism Associated with Neoplasm: Review of Seventy-Seven Cases

Jerrold S. Lieberman, New York, N. Y., Jaime Borrero, Medellin, Colombia, Enrique Urdanetta, Bogota, Colombia, and Irving S. Wright, New York, N. Y.

In a review of approximately 1,500 hospital admissions in which thrombophlebitis was diagnosed, there were 77 cases with neoplasm and thromboembolism. Carcinoma was found in 67 cases. Among these, thrombophlebitis was recurrent or migratory in 31 and involved 3 or more extremities in 9. Thrombophlebitis occurred in one leg in 26 more patients, and in 14 additional patients autopsy revealed undetected thromboses. Of 30 cases treated with anticoagulants, 11 responded well. In 19 there was extension, spread to another extremity, or pulmonary embolization. Some of these refractory thrombophlebitides subsequently responded well to heparin. Three cases developed peripheral gangrene, presumably due to arterial thromboses.

In 32 cases thrombophlebitis occurred prior to the discovery of carcinoma. The interval was greater than 3 years in 4 cases; however, two thirds of the patients had developed thrombophlebitis within the 6 months before diagnosis. Fifteen patients developed thrombophlebitis during the hospital admission at which carcinoma was discovered and 6 thereafter. Pulmonary emboli occurred in 25 patients and caused death in 8. In 13 patients the pulmonary embolus occurred during anticoagulation therapy. In 6 cases the thrombophlebitis began or was exacerbated after the institution of x-ray or chemotherapy. A wide variety of visceral thromboses and infarctions were found at autopsy. There were 4 cases of nonbacterial verrucous endocarditis. The primary carcinoma was most often in the lung (19 cases.) Other sites included pancreas (10), ovary (6), breast (5), colon (5), stomach (5), and prostate (4). In 4 cases the primary site was not determined. In 10 neoplasms other than carcinoma, the clinical findings were similar.

Thromboembolism may occur as a manifestation of a hypercoagulable state associated with neoplasm. The implications of these findings in early diagnosis and more effective management are discussed.

Graham Steell Murmur: A Re-evaluation

William Likoff and Albert N. Brest, Philadelphia, Pa.

The Graham Steell murmur was originally described as a soft blowing diastolic murmur heard along the left sternal border in patients with mitral stenosis. Because of the absence of any associated signs of dynamic aortic insufficiency, i.e., widened pulse pressures or bounding peripheral pulses, Graham Steell postulated that the murmur was probably caused by pulmonary regurgitation secondary to pulmonary hypertension. Since the original description, however, little factual information has been accumulated concerning this bruit. The authors studied 10 patients with early diastolic murmurs along the left sternal border which fit the description of the Graham Steell murmur. The pulmonary artery pressures were normal in 2 of 3 subjects in whom cardiac catheterization was performed. The presence of minor aortic insufficiency was confirmed in 4 patients by retrograde aortography. The absence of pulmonary regurgitation was demonstrated in one instance by pulmonary arteriography. Cardiac exploration provided final conclusive evidence of minor aortic regurgitation and the absence of pulmonary insufficiency in 7 patients in whom cardiac surgery was performed. It would appear that the cause of the early diastolic murmur along the left sternal border in patients with mitral stenosis is due in most instances to adynamic aortic regurgitation rather than secondary pulmonary insufficiency.

Fate of a Patient with a So-called "Mild Coronary"

William Likoff, Leonard Dreifus, and Sheldon R. Bender, Philadelphia, Pa.

The ultimate pathophysiologic manifestation of ischemic heart disease is acute myocardial infarction. Prognostic appraisals of those afflicted are difficult. In these evaluations the term "mild" or "good risk" has come into common usage. It refers to patients who suffer an initial infarction with mild subjective reactions and without arrhythmias, congestive failure, or shock. The myocardial involvement is presumed to be limited to small noncritical areas. The electrocardiographic abnormal-

itus mainly revert to normal within short intervals. In these patients there is a small initial mortality (5 per cent), and they are believed to have the least significant chronic disability and to require the least vigorous therapeutic measures.

One hundred "good risk" coronary patients were observed for 5 years after the initial infarction for the purpose of examining the above premise. The following observations were made: (1) 54 per cent suffered from disabling coronary insufficiency pain after recovery from the infarction; (2) 48 per cent had recurrent myocardial infarctions on an average of 21 months after the initial attack; (3) 82 per cent of those with recurrent infarction were among the group who had persistent insufficiency pain; (4) the recurrent infarction invariably involved the previously afflicted area of the myocardium; and (5) the mortality rate in the recurrence group was 18 per cent.

The data appear to negate the category of a mild or good risk coronary patient, particularly when the pain of coronary insufficiency persists after an initial infarction. They also suggest that in many instances a myocardial infarction is produced by an incomplete evolvement of the responsible factors which then remain poised to redevelop within a short interval. This is a common event in the patient classified as a "mild" or "good risk" coronary.

Surgical Treatment of Aortic and Mitral Valve Lesions Utilizing Prostheses

C. Walton Lillehei, David M. Long, Jr., Robert D. Sellers, and Richard L. Varco, Minneapolis, Minn.

Since 1956 in this clinic all operations on the aortic and mitral valves have been carried out under direct vision utilizing the pump oxygenator. The only exceptions to this policy have been certain patients with pure mitral stenosis who were free of all complicating factors.

This experience has indicated that the basic surgical technics may be divided into three categories: (*a*) reconstruction, (*b*) reconstruction augmented with prosthetic materials, and (*c*) total excision with prosthetic replacement. This presentation concerns the patients in categories (*b*) and (*c*). The substantial majority represents patients with acquired heart disease, but congenital valvular lesions requiring use of prostheses have occasionally been encountered. Approximately 100 patients have left the hospital with various types of partial or total prosthetic valves in the aortic or mitral areas, and the results in these patients have been analyzed with particular respect to surgical technics, design of prostheses, choice of materials, and late follow-up results.

Also described is the value of technics for selective left heart cardioangiography by means of retrograde passage of a catheter into the ascending aorta and left ventricle, both for preoperative planning of the surgical procedure and as a means of objective postoperative assessment of the corrective procedures.

Routine Fluoroscopic Examination of the Heart and Still Photography with Image Intensifier

Wan Ngo Lim, New York, N. Y.

The advantage of fluoroscopic examination of the heart and great vessels is well recognized. Recent emphasis on associated radiation hazard has deterred many cardiac clinics from its use. This report is concerned with a description of the equipment and technic of routine cardiac fluoroscopy with the Image Intensifier and still photography of the normal and abnormal heart in the 3 standard views.

The unit includes (1) a vertical fluoroscope with a 9-inch Image Intensifier and a viewing mirror, (2) a television monitor for group viewing, (3) a camera to take concurrent static films for permanent record, and (4) a motor-driven turntable platform.

A nomogram was formulated from the examination of 100 children, relating time in seconds and radiation exposure to anteroposterior diameter of the chest (range ¼ to 1½ ma., 50 to 60 kv.).

The 9-inch Image Intensifier may be used for routine diagnostic cardiac fluoroscopy with 80 to 90 per cent reduction in radiation hazard compared with conventional fluoroscopy. By adjusting the electron focusing and television contrast, the image obtained is much clearer and sharper than that of the conventional fluoroscope with more detail and much less exposure. Concurrent films for permanent records can be obtained with minimal exposure to patient and examiner.

Ventricular Slowing and Standstill After Spontaneous or Electrically Stimulated Runs of Rapid Ventricular Beats in Atrioventricular Block

Arthur J. Linenthal, Paul M. Zoll, Garo H. Garabedian, and Karin Hubert, Boston, Mass.

Idioventricular slowing after runs of rapid ventricular beats has been a much-needed but heretofore unavailable index of the stability of ventricular pacemakers in keeping the heart free from Stokes-Adams attacks. Relatively rapid ventricular activity was produced in dogs with experimental heart block and in 5 patients with Stokes-Adams disease by external electric stimulation and by spontaneous tachycardia.

The amount of ventricular depression, measured by the longest ventricular pause, was directly related to the rate and duration of the tachycardia.

Ventricular standstill for 15 seconds was observed in the dog after electric stimulation for 1 minute at 180 per minute and in 1 patient after stimulation for 15 seconds at 60 per minute. Return of the idioventricular rate to prestimulation levels was practically complete within 20 seconds.

The ventricular slowing was strikingly decreased by epinephrine and isoproterenol, which are the most potent drugs available for arousal, acceleration, and maintenance of ventricular pacemakers; dichlorisoproterenol, a potent sympathomimetic blocker, blocked these effects. Ephedrine, which is valuable in preventing Stokes-Adams attacks although it has little effect on the idioventricular rate in the dog and in man, markedly reduced the ventricular depression. Methoxamine, which slows the idioventricular rate, markedly lengthened the pauses after electric stimulation.

This ventricular depression provides a technic for studying various aspects of cardiac impulse formation, an explanation for some types of Stokes-Adams attacks (ventricular standstill following transient atrioventricular conduction), and a useful clinical guide to the prediction of attacks and to the efficacy of drugs in their prevention.

Distensibility of the Human Left Atrium

Chi Kong Liu, Ronald T. Piccrillo, Torrance, Calif., and Myrvin Ellestad, Long Beach, Calif.

Direct and indirect left atrial pressure tracings obtained by several methods were used to differentiate significant mitral insufficiency from mitral stenosis in combined mitral insufficiency and stenosis.

Methods of analyzing the pressure pulse tracings are discouraging in many cases. This study was designed to evaluate the distensibility of the human left atrium. The left atrium was obtained 8 to 24 hours after death. A rubber balloon of over 1,000 ml. capacity was introduced, and 2 outlets of the balloon were inserted into the pulmonary veins. The mitral valve was closed with continuous sutures. The heart was suspended in Ringer's solution at room temperature. The volume of the left atrium was measured at 0 pressure. Ringer's solution was then injected at a constant rate of flow (76.4 cc. per minute) and the pressure recorded. In 7 subjects the average volume of the left atrium was 34 ml. at 0 mm. Hg. It required 34 ml. to increase the pressure from 0 to 10 mm. Hg, 10.6 ml. from 10 to 20 mm. Hg, and 5.4 ml. from 20 to 30 mm. Hg. When the pressure of the left atrium was higher, the organ was less distensible. The results of this study may be helpful in the interpretation of left atrial pressure pulses in patients with combined mitral lesions.

Both atrial distensibilities were also compared in this study.

High-Frequency Phonocardiography

Aldo A. Luisada and Giuliano Di Bartolo, Chicago, Ill.

A systematic study of the high-frequency (H.F.) components of heart sounds and murmurs was carried out by means of a new standardized and calibrated phonocardiograph provided with a variable band pass filter. The frequency bands 500 to 1,000 c.p.s. and higher were particularly studied, but comparison was also made with the vibrations found in lower bands.

This study covered 47 subjects, including 5 normal or borderline cases.

The groups of H.F. vibrations were normally shorter than the equivalent group of lower bands; they usually appeared at the beginning of equivalent vibrations, and they often presented a relative increase of amplitude.

Several clinical phenomena were better revealed by the study of H.F. bands, including the physiologic or pathologic splitting of the first and second sounds, the opening snap, and certain murmurs. The H.F. bands often revealed more clearly the "shape" of a murmur. In some cases splitting of the heart sounds or the existence of a murmur was revealed only by these bands.

In about one fourth of the cases, the first sound was comprised of 2 simple vibrations (or groups of vibrations). These were identified as coinciding with mitral closure and aortic opening. One of the 2 may disappear in the highest band.

In more than one third of the cases, the second sound was made up of 2 simple vibrations (or groups of vibrations). These were identified as coinciding with aortic closure and pulmonic closure. The latter usually disappeared in the highest band except in cases of pulmonary hypertension.

The optimum and maximum frequency bands were studied for the 4 sounds, both in normal subjects and clinical cases. A similar study was done in connection with the "ejection sound" and the opening snap of the mitral valve.

Murmurs recorded in the H.F. range either disappeared, or were still present, or became more clearly visible. The murmurs of mitral and aortic insufficiency were usually in the last group and were sometimes recorded only in the H.F. range.

Simple Technic for Apical Catheterization of the Left Ventricle in Infancy and Childhood

Paul R. Lurie, Robert M. Armer, and Eugene C. Klatte, Indianapolis, Ind.

Twelve patients with aortic stenosis and 2 with pulmonic stenosis combined with complete transposition were studied. There was one failure to pass through the semilunar valve. One patient developed a small myocardial infarction due to

false passage of the needle. In every case valuable new information was obtained.

Technic: The patient is placed supine or in a right anterior oblique position on a table equipped for cinecardioangiography. The apex is located by palpation and fluoroscopy. After local anesthetic a 5 mm. stab wound of the skin is made one interspace below the apex. An 18-gage, thin-walled needle with movable needle stop is advanced through the wound and the cardiac apex in an upward and backward direction. The stylus is removed, and a soft-tipped Seldinger guide wire, 80 cm. long, is inserted through the needle and passed out the semilunar valve. The needle is removed. Over the proximal end of the guide wire a length of 19-gage thin-walled Teflon tubing is advanced up to the wound. Wire and Teflon are advanced together through chest wall and myocardium until the distal end of the tubing is beyond the semilunar valve. The wire is removed, and pressure is measured above the valve, contrast injected, pull-back pressure recorded, contrast injected below the valve, with further pressure pull-back toward the apex and contrast injection being made as necessary.

The catheter may be advanced back out the semilunar valve or through the mitral valve as necessary and contrast injections made in other projections if desired, but there is some added risk from bleeding and arrhythmia. Without change of position and with only retraction of the catheter, these complications have not been troublesome.

Basal Diastolic Murmur—Clinical Study of Eighty-One Patients with Rheumatic Heart Disease

Melville G. Magida, Stamford, Conn., and David M. Roseman, New York, N. Y.

This study concerns 72 patients, ages 20 to 50, who have been followed since childhood. Basal diastolic murmurs with mitral valve disease were present in all. The group comprised 2 major categories: (1) those with a basal diastolic murmur and increased pulse pressure (41 patients, 22 living and 19 deceased) and (2) those with a basal diastolic murmur without concomitant increase in pulse pressure (31 patients, 16 living and 15 deceased). Examination included electrocardiograms, fluoroscopy in posteroanterior and oblique projections, phonocardiograms, and radial pulse tracings.

Of the 41 patients in group 1, the majority were asymptomatic. Most of these had marked cardiac enlargement which was related to the occurrence of carditis. Deaths in this group were attributable to carditis in 9, subacute bacterial endocarditis in 3, and progressive deterioration of cardiac reserve in 7. These patients were asymptomatic for an average of 13 years before the occurrences which led to their deaths. In group 2 the majority were asymptomatic. Eighty-one per cent had marked and the remainder moderate cardiac enlargement. The increase in heart size occurred with or very shortly after an episode of carditis. Deaths in this group were attributable to heart failure in all but 2 who died of subacute bacterial endocarditis. All had marked cardiac enlargement. These patients were asymptomatic for an average of 17 years.

It is concluded that significant aortic insufficiency even with marked cardiac enlargement is compatible with many years of freedom from symptoms.

Cardiac Output Response to Exercise in Normals and Patients with Arteriosclerotic Heart Disease

Donald V. Mahony, Fullerton, Calif.

The determination of cardiac output before and after exercise is significant in the evaluation of myocardial reserve power. Cardiac output studies have been somewhat restricted because of the relatively complicated equipment and clinical procedures necessary to perform the test when using the Fick or Evans blue dye methods.

It was the purpose of this study to determine the cardiac output at rest and after a standard exercise test. Cardiac output was obtained from a precordial dilution curve after the rapid intravenous injection of radioactive human serum albumin.

Cardiac output before and immediately after exercise was investigated in 32 patients without any evidence of cardiovascular disease and in 58 patients with definite arteriosclerotic heart disease. The mean increase with exercise was 71 per cent in the normal group and 28 per cent in the abnormal group. A normal individual should be able to increase his cardiac output from 50 to 150 per cent after exercise. A response of less than 50 per cent increase with exercise is considered abnormal.

Further distinguishing characteristics between the groups was found in a review of the cardiac output curves. Patients with arteriosclerotic heart disease may have abnormal prolongation of the build-up or disappearance times before or after exercise. This type of simple test seems to be helpful in differentiating between a normal and abnormal cardiovascular system by demonstrating a patient's myocardial reserve.

Treatment of Experimental Respiratory Acidosis by Extracorporeal Circulation

Felice Manfredi† and Herbert O. Sieker, Durham, N. C.

Acute respiratory acidosis with CO_2 intoxication occurs commonly in pulmonary insufficiency. Its treatment with bronchodilators, mechanical respirators, and buffering agents may be unsuccessful. This experimental study was undertaken to investigate the possibility that hypercapnia and acidosis could be rapidly corrected by passing venous blood through a small bubble-type oxygenator in which CO_2 is removed.

In 11 dogs a venous-venous bypass was created using a special double-lumen catheter (inserted through a femoral cutdown into the inferior vena cava), a reservoir, a Sigmamotor pump, and an oxygenator with low oxygen flow. Blood flows of 300 ml./min. were maintained through this system. CO_2 tensions of blood going to the oxygenation chamber (V pCO_2) were altered by changing the CO_2 concentration of inspired air.

At constant blood flows, the CO_2 removed was found to be dependent on V pCO_2. When V pCO_2 was increased from 20 to 75 mm. Hg, the CO_2 extraction rose from 2.2 to 26.7 vol./100 ml. blood/min. Greater rates of removal were not observed with further increase in V pCO_2 up to 127 mm. Hg. In acidotic animals, after one hour with the extracorporeal circulation, arterial pCO_2 was maintained at levels 14 mm. Hg lower than during control.

An extracorporeal blood flow of 300 ml./min. with a V pCO_2 of 75 mm. Hg removes 80 ml. of CO_2 per minute. In experimental animals this represents approximately 80 per cent of total CO_2 production per minute. These observations suggest that extracorporeal circulation may be useful in correcting hypercapnia and acidosis in patients with CO_2 intoxication.

Mechanical Events During Anomalous Atrioventricular Excitation (Wolff-Parkinson-White Syndrome)

Harold W. March, Palo Alto, Calif., Arthur Selzer, San Francisco, Calif., and Herbert N. Hultgren, Palo Alto, Calif.

The clinical and electrocardiographic features of anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome) have been extensively studied, but the mechanical consequences of this abnormality have received less attention. Since the sequence of ventricular contraction may provide important clues to the basic mechanism of the syndrome, 12 patients with anomalous atrioventricular excitation were studied by means of phonocardiograms, carotid stethograms, and in one instance by cardiac catheterization. In 3 cases studies were possible during both normal and anomalous excitation so that the patient acted as his own control.

In 5 instances mechanical abnormalities were detectable. These abnormalities were varied and consisted in one case of the early onset and completion of ejection in both ventricles and in one case of early completion of ejection in the left ventricle. This was demonstrated by comparing events during anomalous and normal excitation. In 3 cases there was delayed onset of contraction on the contralateral side and possibly on the homolateral side as well. The remaining 7 cases showed no mechanical abnormalities by the methods employed.

These observations suggest that the effect of anomalous excitation on the mechanics of the heart is variable and that 2 mechanical varieties of the Wolff-Parkinson-White syndrome exist. In one there is demonstrable ventricular asynchrony, whereas in the other there is no evidence of such asynchrony. It may not be possible to distinguish between these 2 varieties by clinical and electrocardiographic methods, but the detection on auscultation of broad or paradoxic splitting of the second sound is suggestive. The variable mechanical effects may be ascribed to differences of transmission time through the A-V node and to the site of entrance of the excitatory impulse from the anomalous pathway.

Pulmonary Compliance in Congestive Heart Failure

Jack M. Martt, Columbia, Mo.

Although a decrease in pulmonary compliance in patients with heart disease is frequently alluded to, there are few studies in subjects with heart disease other than in patients with mitral stenosis or cor pulmonale. Therefore, 12 patients with congestive heart failure secondary to arteriosclerotic and/or hypertensive heart disease were selected for study. Cardiac output was determined by the dye-dilution technic. On completion of therapy both pulmonary compliance and cardiac output were again determined.

In 19 subjects serving as controls, the values were 0.13 to 0.23 L./cm. water. Patients with congestive failure revealed a consistently decreased compliance with values from 0.06 to 0.14 L./cm. water, and invariably there was an increase after therapy. The technic employed for determination of lung compliance is more simple than many of the methods currently in use.

It is apparent that alteration in pulmonary compliance plays an important role in the production of dyspnea in congestive heart failure and is invariably altered in this clinical syndrome.

Electrocardiographic Effects of Hypo- and Hypermagnesemia

Jack M. Martt, Constantine Anast, Akgun Sayman, and John Laird, Columbia, Mo.

This study was conducted to determine the electrocardiographic manifestations (if any) of a low serum magnesium. Twenty dogs were connected to an artificial kidney, and extracorporeal dialysis was carried out for 4 to 8 hours, using a magnesium-free dialysate. Six animals served as controls. Frequent electrocardiograms were obtained, as well as serial measurements of serum magnesium, potassium, sodium, calcium, chloride, and bicarbonate, and arterial oxygen content, arterial pH, and arterial blood pressure.

Serum magnesium decreased rapidly, the lowest level occurring after 3 to 4 hours of dialysis. No specific electrocardiographic alterations could be attributed to hypomagnesemia. However, after production of hypermagnesemia with intravenous magnesium solutions, electrocardiographic abnormalities were observed, consisting of first degree atrioventricular block, shortening of Q-T interval, and bradycardia.

Low Frequency-Intensity Analysis of Heart Sounds in Coronary Artery Disease

Daniel Mason, Norman B. Burke, Lawrence P. Devlin, Ahmed Usman, and Giampiero Bartolucci, Philadelphia, Pa.

By means of a specially designed barium titanate microphone capable of recording in the low frequency range, the heart sounds in a group of 300 patients with normal hearts (as determined by the usual clinical criteria of history, physical examination, electrocardiogram, and teleoroentogenogram) and in another group of 75 patients with coronary artery disease (acute and chronic) were recorded from the precordium onto magnetic tape. The age groups were arbitrarily subdivided as follows: 25 to 35 years, 36 to 45 years, 46 to 55 years, 56 to 65 years, and 66 to 75 years.

These recordings then were subjected to low frequency-intensity analysis (spectrograms) by means of low pass and band filters.

Results revealed a significantly different frequency-intensity pattern in the first heart sound of the normal patient group compared with that of the coronary artery disease group.

Age, sex, and habitus did not appear to influence the normal pattern of the first heart sound.

The most significant difference between the normal and abnormal group appeared to be in the 35 to 50 c.p.s. range. In those with normal hearts the pattern of the first heart sound revealed greater intensity "peaking" and more clear-cut frequency oscillations compared with the coronary patient group. Of interest was the demonstration of abnormal patterns in some of the "normal" patients suggesting that these individuals might have occult coronary disease.

Frequency-intensity response of the first heart sound in the 35 to 50 c.p.s. range may well depend to some extent on the "integrity" of the ventricular musculature.

Release of Renal Pressor Substances in Hypertensive Rats

George M. C. Masson and Teruo Omae, Cleveland, Ohio

Renal pressor substances in hypertension were measured by grafting kidneys on 24-hour nephrectomized rats. Two procedures were used. In the first, the renal vascular pedicle was cannulated and the kidney perfused with saline and connected to the femoral blood vessels of the nephrectomized rat. In the second, interruption of circulation and washing were avoided by anastomosing the femoral vessels of the nephrectomized rat with aorta and cava of the hypertensive rat. Hypertension was produced by renal infarction, renal artery constriction, renal encapsulation, desoxycorticosterone treatment, and adrenal enucleation. Grafting of a normal kidney elicited a pressor response which varied with the operative procedure. With the first method, it consisted of a sharp rise followed by a slight decrease and a plateau; with the second procedure, there was also an initial rapid rise, then a gradual and slow increase suggesting a continuous "secretion." Infarcted and encapsulated kidneys, as well as those from rats with hormonal hypertension or on a high-salt diet, did not release any pressor material. In hypertension due to arterial constriction, pressor substances were released by the clipped but not by the contralateral "normal" kidney. These results are in general agreement with those obtained by other investigators from determination of the "renin" content of kidneys, which was found to be high normal in a clipped kidney, low in the unclipped kidney, and absent in DCA hypertension. Also the results suggest that hypertension due to clamping of the renal artery may be unique in its pathogenesis, differing from that due to other renal manipulations.

Predictive Tests in Unilateral Renal Hypertension: Critical Analysis of Twenty-Five Operated Patients

Morton H. Maxwell, Robert E. Rockney, Chester C. Winter, and Charles R. Kleeman, Los Angeles, Calif.

Twenty-five patients have been followed for at least one year after surgery for unilateral renal hypertension. Fourteen are normotensive (cured group); 7 exhibit marked reduction of preoperative blood pressure (improved group); 4 have unchanged blood pressures (failures).

Diagnoses were almost equally divided between unilateral atrophic pyelonephritis and occlusive

disease of the renal arterial vasculature. Severity ranged from moderate to accelerated hypertension. The distribution of diagnoses and severity was similar in all groups. Radioactive renogram was positive (unilateral abnormality) in 12 of the cured group, 4 of the improved group, and all 4 of the failures; it was negative in 2 of the cured and 2 of the improved patients. The intravenous urogram was positive in 10 and negative in 3 of the cured group, positive in 4 and negative in 3 of the improved, and positive in 2 and negative in 2 of the failures. The aortogram was positive in 9 and negative in one cured patient, positive in 4 and negative in 2 improved subjects, and positive in the one failure in whom it was performed. Tetraethyl ammonium chloride infusions (TEAC test) were positive in the 3 cured patients in whom it was done. Split function tests disclosed overall renal hemodynamics characteristic of hypertension and unilateral renal impairment in all subjects. Positive "Howard tests" were obtained in 5 cures and 2 improved patients; negative tests were obtained in 3 cures, 2 improved, and one failure. Nonfunctioning kidneys or technical difficulties precluded evaluation of the Howard test in the remainder.

Of greatest predictive value in these patients was a "suspicious" history (unusual age for essential hypertension, sudden onset or acceleration of hypertension). There is as yet no single clinical test which is uniformly predictive of operative cure or improvement in unilateral renal hypertension.

Emotion and Blood Coagulation

George A. Mayer and W. Ford Connell, Kingston, Ontario, Canada

A total 407 patients on prolonged anticoagulant therapy have been followed for periods of one to 6 years. The anticoagulants have been controlled by the authors' standard clotting time. Eighty-seven per cent of these patients showed a stable anticoagulant effect within 6 to 8 weeks, permitting lengthening of the interval between control tests to 4 or 5 weeks. Thirteen per cent exhibited a "brittle" anticoagulant effect. The patients in this group were all emotionally labile and exhibited frequent outbursts of acute anxiety. During such phases previously adequate anticoagulant dosage became inadequate with shortening of the standard clotting time. In some this effect of acute anxiety became manifest within 2 or 3 hours; in these cases the possibility of altered gastrointestinal absorption of the drug could be eliminated. Emotionally unstable patients on anticoagulant therapy need frequent control tests to avoid excessive or inadequate treatment. They should be advised to report at once without appointment for a check of their therapeutic control whenever they are under emotional stress.

Tocopherol in the Atherosclerotic Human Aorta

Eugene C. McCormick, Conway Springs, Kans., and Robert H. McCluer, Columbus, Ohio

Tocopherol would be expected to be deposited in atheromas since this lipid antioxidant has been shown in this laboratory to be transported principally by the atherogenic, low-density lipoproteins.

In the present study tocopherol in the free, ester, and quinone forms was determined in normal and atherosclerotic aortas. Over 85 per cent of the Emmerie Engel reducing substance in the nonsaponifiable fraction was demonstrated to be tocopherol or tocopherol quinone by spectral analysis of chromatographically purified samples. The total tocopherol content of aortas was 2 to 3 mg./Gm. wet tissue in normal and up to 16 mg./Gm. in severely atherosclerotic aortas. The tocopherol to cholesterol ratio was similar in normal and atherosclerotic aortas, as well as in isolated atheromas, the mean ratio being 0.0046. This ratio is close to that found in normal plasma. The percentage of quinone (12 to 36) was also close to that of plasma. No tocopherol ester was found. Tocopherol, measured by its antioxidant capacity in terms of β-carotene half-life in the presence of excess hydroperoxide, was 97 to 104 per cent of the chemically assayed tocopherol content. There was no indication of tocopherol toxicity in the aortic lipid extracts.

In view of the tocopherol-cholesterol ratio, carotenoid-cholesterol ratio, percentage of quinone, and antioxidant capacity of atherosclerotic aortas, there appears to be adequate tocopherol in atheromas to prevent lipid peroxidation. Therefore, the reported existence of lipid peroxides in atheromas is inconsistent with the lipid antioxidant role of tocopherol.

Congestive Heart Failure in Infancy

Carolyn M. McCue and Reuben B. Young, Richmond, Va.

An infant in congestive heart failure is a true pediatric emergency. A clinical review of 115 consecutive cases of heart failure in infants under 2 years of age admitted to the Medical College of Virginia Hospital in a 7-year period was undertaken in order to emphasize the serious prognosis and to stress the importance of early definitive diagnosis and treatment.

According to rigid criteria for diagnosis of heart failure in infancy, dyspnea was present in all cases, cardiac enlargement in 90 per cent, and

patomegaly in 85 per cent. Heart rates over 0 and rales were each found in over 60 per cent.

The 5 most common congenital lesions causing ilure were interventricular septal defects (13), arctation of the aorta (12), transposition of eat vessels (11), patent ductus arteriosus (9), d aortic atresia (7). The mean age of onset symptoms was 3 days for aortic atresia, 1 nth for coarctation, 1½ months for transposion, 3 months for ventricular defects, and 4 nths for patent ductus. Emphasis is placed remediable lesions, their immediate treatment, agnostic studies, and early surgical correction.

Primary endomyocardial disease occurred in 30 ses, of which 8 died at a mean age of 2 months with endocardial fibroelastosis. Thirteen still survive, presumably with healing myocarditis.

Rarer, but responding to treatment were paroxysmal tachycardias (3) and severe anemias (3) with hemoglobin under 2 Gm.

Of the group of 115 infants, 41 patients are living, a 64 per cent mortality. Seventy-four died, and 86 per cent had necropsy studies. A prompt, positive approach to both medical and surgical therapy should improve mortality rates.

Eight-Year Evaluation of the Dammann-Muller Procedure

James A. McEachen and Rodney T. Smith, Santa Monica, Calif.

Before the advent of open intracardiac surgery Dammann and Muller advocated narrowing of the main pulmonary artery for patients with large left-to-right intracardiac shunts. Of the original group of patients on whom they performed this procedure, 7 have been closely followed for 8 years. Clinical observations included an early decrease in heart size, subsidence of cardiac failure, decrease in the frequency of respiratory infection, and considerable improvement in growth and development. There have been no late mortalities. One patient whose stenosis was considered excessive developed severe cyanosis. Postoperative cardiac catheterization demonstrated pressures in the pulmonary artery distal to the point of narrowing which varied from 20/3 to 47/16. Right ventricular pressures were systemic or very slightly lower. With the exception of one patient whose stenosis was excessive, all patients demonstrated moderate-sized residual left-to-right shunts, and systemic saturation varied from 86 to 96 per cent. Four of these patients have undergone successful reconstruction of their pulmonary artery and closure of the ventricular septal defect with the aid of cardiopulmonary bypass and profound hypothermia.

With increased experience the mortality of the procedure has decreased to approximately 10 per cent, as reported by Dammann. At the present time, in view of the high mortality associated with the closure of ventricular septal defects in infants, it is the authors' opinion that initial narrowing of the main pulmonary artery provides a lifesaving, palliative measure for the infant with a large left-to-right shunt producing cardiac failure and permits the patient to attain sufficient size for a safe corrective operation.

Validity of Employing the Vasodilated Ear and a Modified Oximeter for the Measurement of Cardiac Output by Dye-Dilution Curves

Maurice McGregor, Paul Sekelj, Montreal, Canada, and William S. Adam, Belfast, Ireland

A dye-dilution method was tested for measuring the cardiac output without the necessity of arterial puncture or the analysis of venous "end-tail" samples. It employs a modified ear oximeter and Coomassie blue dye. This method of calibration has proved accurate when checked against venous "end-tail" samples. A study was made of the inherent characteristics of the ear as a recording site for a time-concentration curve. In 14 subjects 51 injections were made of Coomassie blue dye at rest and during increasing exercise loads up to 700 Kg./M./min. Simultaneous time concentration curves were inscribed using an arterial cuvette and the ear oximeter. Comparison was made of the time components of the 2 curves and of the cardiac output computed from each. Although the transit time differed by less than 20 per cent, in only 58 per cent of studies the cardiac outputs compared well. Cardiac output ranged from 3.0 to 18.6 L. per minute. There was no systematic difference between the output computed by the 2 methods, and the individual differences never exceeded 20 per cent. The criteria for a "valid" ear curve were studied and redefined. By the method employed it was possible to measure cardiac output repeatedly and with reasonable accuracy with an ear oximeter and a peripheral venous injection of blue dye without the use of "end-tail" sampling.

Differential Diagnosis of Continuous Murmurs Suggesting a Patent Ductus Arteriosus

Henry D. McIntosh, Julian C. Sleeper, Howard K. Thompson, Jr., William F. Barry, and Edward S. Orgain, Durham, N. C.

A continuous murmur in the left upper chest is usually considered diagnostic of a patent ductus arteriosus. Other less common cardiovascular abnormalities accompanied by similar murmurs may be confused with ductus arteriosus, i.e., aortic pulmonary window, ruptured sinus of Valsalva, coronary A-V fistula, increased collateral circulation to the lung, total anomalous pulmonary venous drain-

age, isolated pulmonary artery stenosis, and others. Except for isolated pulmonary artery stenosis these lesions are accompanied by shunts, usually left-to-right. Correct diagnosis depends on precise localization of the level of the shunt.

Eight patients with continuous murmurs but with atypical location or transmission for a classic patent ductus arteriosus have been extensively studied. The diagnosis was confirmed at surgery in 6 and appears unequivocal in the 2 unoperated patients. Two had ductus arteriosus, the others less common defects. The correct diagnosis was obtained only after simultaneous right and left heart catheterization with dye (indocyanine) injection into selected sites of the left heart and aorta, sampling from the right heart and pulmonary arteries, and selective contrast cinefluorography. Cinefluorography usually confirmed the presence of the shunt. In 4 patients, although the presence of a shunt was demonstrated, precise localization could not be made by radiographic technics alone; in 4 the correct diagnosis could not have been made with certainty without radiographic technics.

This study demonstrates that in some patients with confusing continuous murmurs both dye dilution and radiographic technics are required for precise diagnosis. The preoperative studies (including the cinefluorograms) were done in a patient with a coronary A-V fistula to the right atrium, a patient with a sinus of Valsalva aneurysm ruptured into the right ventricle, and in a patient with sequestration of the lung with systemic collateral circulation to the lung.

Serum Lipids and Arteriosclerosis in Prostatic Cancer Patients

George F. Meissner and Constance C. Moehring, Providence, R. I.

In order to test the hypothesis that castration and estrogen therapy in men lead to serum lipid changes accompanied by amelioration of arteriosclerosis, serum lipids were determined periodically in 163 patients with prostatic carcinoma. These were treated for periods of 4 months to 2½ years by orchiectomy and estrogens, generally resulting in gynecomastia. Twelve of these patients have come to autopsy. Their coronary arteries and aortas were evaluated grossly for the degree of arteriosclerosis, and particular attention was paid microscopically to the presence or absence of "early and active" lesions. The gross specimens are being saved for a simultaneous final grading at the conclusion of the study.

To date, it would appear that there were only slight serum lipid changes which could be considered a result of castration or estrogen therapy and that there was no definite correlation between these and the indications of arteriosclerosis found at autopsy. A series of 10 untreated prostatic cancer patients found at autopsy during the same period showed no significant difference as to the degree of arteriosclerosis when compared to the treated cases.

Production of Acute Pulmonary Edema by Methylene Blue in the Dog

Ramon P. Mendiola, Fletcher A. Miller, and Francisco Grande, Minneapolis, Minn.

Intravenous injection of methylene blue at a dose of 40 mg./Kg. of body weight has been found to produce consistently an acute pulmonary edema in the intact dog. Death occurred between 10 and 40 minutes after the injection with the usual signs of pulmonary edema. The mean weight of the lungs of 8 dogs dead from pulmonary edema after methylene blue injection was 21.1 Gm./Kg. body weight. Administration of methylene blue at a dose of 2 mg. or more per 100 ml. of blood also invariably produced pulmonary edema in the perfused dog's lungs. Twenty minutes after the administration of 4 mg. of methylene blue per 100 ml. of blood into the perfusion system, the weight of the lungs was 27.0 Gm./Kg. body weight. A relationship appears to exist between the dose of methylene blue and the speed of development of the edema. Recording of the blood pressure in the system perfusing the pulmonary artery showed very small or no changes of vascular resistance in the lung after the injection of the usual edema-producing doses of methylene blue. However, when very high doses of dye were added to the perfusion blood (40 mg./100 ml. of blood), a marked increase of the pulmonary artery pressure (50 mm. Hg) was observed. The weight of the lungs 20 minutes after administration of this dose of methylene blue in one experiment was 48 Gm./Kg. of body weight. It is concluded that methylene blue produces acute pulmonary edema in the dog with only minor hemodynamic changes in the pulmonary circulation.

Digital Vascular Reactivity to Hypertensin II in Normotensive Subjects and in Patients with Primary Hypertension

Milton Mendlowitz, Nosrat Naftchi, Robert L. Wolf, and Stanley E. Gitlow, New York, N. Y.

Digital arterial blood pressure and digital blood flow were measured in 15 normotensive subjects and 15 patients with primary hypertension in 3 phases: (1) under standardized conditions at rest; (2) after vasodilatation by indirect heating supplemented by the intravenous injection of a ganglion-blocking drug (SC 1950); (3) after continued indirect heating and the intravenous in-

sion of additional SC 1950 and hypertensin II a rate sufficient to increase the blood pressure oderately. Systolic and diastolic pressures were easured by the flush-throb method using a aertner capsule, and blood flow was measured lorimetrically. The flow-pressure ratios and the ressures were used to calculate work of vasoconriction per microgram of hypertensin II infused er minute.

The hypertensive patients were considerably ore reactive to hypertensin II than the normonsive subjects. If renal hypertension is caused y hypertensin II, equivalent secretion of this ubstance would increase the blood pressure more n patients with essential hypertension than in patients without this disease.

Reflex Coronary Constriction: Its Possible Existence in Human Congestive Heart Failure

Joseph V. Messer, Herbert J. Levine, William A. Neill, Richard J. Wagman, and Richard Gorlin, Boston, Mass.

Coronary and systemic hemodynamics were measured in 44 patients. Twenty-two controls had normal coronary hemodynamics without congestive heart failure, 7 patients had coronary artery disease without congestive failure, and 15 had congestive failure, of whom 6 had normal coronary circulation and 9 had coronary insufficiency elicited by exercise.

In controls rest and exercise myocardial oxygen consumptions (MqO_2) were met entirely by coronary blood flow with fixed coronary venous oxygen content (CVO_2) and myocardial oxygen extraction (A-V O_2/AO_2). Resting coronary artery disease patients without congestive failure resembled controls in all parameters, although during exercise A-V O_2/AO_2 increased 9 per cent and CVO_2 fell 21 per cent, indicating inadequate coronary blood flow relative to MqO_2.

At rest congestive failure patients with a cardiac index above 3 L./min./M.^{2} supplied an increased MqO_2 by increased coronary blood flow with normal CVO_2 and A-V O_2/AO_2. By comparison, resting congestive failure patients with coronary index below 3 had an 11 per cent greater A-V O_2/AO_2, 32 per cent lower CVO_2, 19 per cent greater coronary vascular resistance, and a 2[illegible] per cent greater systemic vascular resistance. All congestive failure patients had sufficient coronary vasodilatation on exercise to exclude coronary insufficiency at rest. In all failure patients without insufficiency A-V O_2/AO_2 and CVO_2, whether normal or abnormal at rest, remained constant during exercise indicating coronary blood flow adequate to an increased MqO_2.

In low output congestive failure an increased A-V O_2/AO_2 persisting but not increasing in the presence of exercise coronary dilatation suggests that reflex coronary constriction exists. The coexistence of increased coronary and systemic vascular resistance in such patients suggests coronary participation in the vasoconstriction of low output congestive failure. The resultant reduced coronary blood flow may be important in the pathophysiology of congestive heart failure.

Do Lymphatic Vessels Exist in the Heart Valves of the Dog?

Albert J. Miller, Ruth Pick, and Louis N. Katz, Chicago, Ill.*

The presence or absence of lymphatic vessels in heart valves remains a question. In the course of our studies we have had the opportunity to investigate this problem.

The mitral valves from three groups of dogs were studied: (1) stock dogs killed during the course of other laboratory experiments; (2) "sham"-operated dogs; and (3) dogs in which surgical obstruction of cardiac lymphatic drainage was produced and which were then killed at varying periods of time after surgery.

Only an occasional thin-walled channel was found on histologic study of the mitral valve leaflets in the control and "sham"-operated animals. However, in dogs subjected to chronic interference of the lymph drainage of the heart, there were numerous such thin-walled channels.

These channels, which become numerous and dilated after obstruction of cardiac lymph flow, are considered to be lymphatics. The implications of the presence of valve lymphatics in relation to inflammatory processes in human hearts (e.g., rheumatic fever, myocarditides) may be considerable.

Incidence and Nature of Streptococcal Infection in Adult Rheumatic Heart Disease as a Basis for Penicillin Prophylaxis

Joseph M. Miller, Paul Fremont-Smith, and Rose L. Breihahn, Boston, Mass.

The purpose of this study was to appraise the incidence, nature, and consequences of streptococcal infection among adult patients with rheumatic heart disease. Since such infection can be responsible for recrudescence of acute rheumatic fever, measurement of the risk of streptococcal infection in older patients should provide a more rational basis for chemoprophylaxis requirements in late adult life.

Seventy-eight adults with rheumatic heart disease did not receive chemoprophylaxis but instead were observed at monthly intervals over 4,680 patient-weeks (1957-1960). Throat cultures and antistreptolysin-O determinations served as indices of streptococcal infection. Acute respiratory dis-

ease occurring between clinic visits was similarly documented. In addition, 68 adults with coronary artery disease were studied in like manner over 2,860 patient-weeks and provided a comparison group lacking the unique risk of streptococcal infection attributed to rheumatic patients.

Eight streptococcal infections occurred in each group, yielding attack rates (per 1,000 patient-weeks) of 1.7 in the rheumatic patients and 3.6 in the comparison group. Streptococcal antibody response was generally weak, and the highest titer in all subjects did not exceed 400 Todd units. No rheumatic fever recurrences were observed.

These limited observations suggest that there is no unusual predisposition to streptococcal infection in older rheumatic subjects and a strikingly lower incidence than in children. Antibody titers also indicate major differences from the antigenic stimulation pattern of children. Such findings help explain age variables in the development of acute rheumatic fever and have implications for the assessment of the need for chemoprophylaxis.

Effects of Tilting on Pressures, Flow, and Volume in the Pulmonary Vascular Bed

William R. Milnor and Charles J. McGaff, Baltimore, Md.

Measurements in our laboratory indicating that normal average pulmonary blood volume (PBV) in man is about 250 ml./M.^{2} are difficult to reconcile with previous reports, based on less direct methods, that relatively large amounts of blood shift from the extremities to the lungs with a change from the erect to supine position.

In 8 patients with rheumatic mitral stenosis, PBV, cardiac output, and pulmonary artery, left atrial, and brachial artery pressures were measured first in the supine position and then after 15 minutes in a semierect position (passive tilting of table foot down, 30 or 45 degrees from horizontal).

Arterial dye-dilution curves, after successive injections into the pulmonary artery and left atrium, were used to measure PBV. Pulmonary mean transit time was measured by subtracting pulmonary to brachial artery from left atrium to brachial artery mean transit time, and PBV was calculated by multiplying cardiac output and pulmonary mean transit time.

Changes in PBV with tilting were not significant, amounting to less than 60 ml./M.^{2} in 7 cases. Pulmonary artery pressure fell consistently (average 10 mm. Hg), as did left atrial pressure (average 10 mm. Hg). Pulmonary vascular resistance (PVR) did not change significantly in 7 cases. Cardiac index decreased slightly.

The absence of changes in PVR and failure of PBV to decrease with tilting may reflect relative rigidity of the pulmonary vascular bed in these patients. The response of normal subjects has not been tested in the same way, however, and it may be that blood distribution between pulmonary and systemic circuits is actually relatively insensitive to changes in body position.

Effective Vasomotor Tone, Prevention of Vasodilatation with Carbon Dioxide During Open Heart Surgery

James B. Minor, William A. Hopkins, William C. Wansker, Lester Rumble, Jr., Richard C. King, and M. Bedford Davis, Atlanta, Ga.

In open heart surgery during extracorporeal perfusion, variable periods of arterial hypotension have been reported. Since this response has occurred despite careful attention to blood loss and during high flow body perfusion, it would seem that the vasodilatation is chiefly related to decreased peripheral resistance.

In previous animal work in which refractory shock had been produced and an extracorporeal circulation utilized, a similar vasodilatation was observed. This occurred despite good oxygenation and the maintenance of an adequate arterial pump output (75 ml./Kg./min.). During oxygenation it was found that CO_2 washout occurred, and if this was corrected, the arterial pressure drop could be prevented.

The effects of variable concentrations of CO_2 (3 to 20 per cent) on the pressure dynamics during cardiac bypass were studied in 60 open heart surgery patients, using occlusive roller pumps and a disc oxygenator with low flow body perfusion (35 to 65 ml./Kg./min.).

Simultaneous and equally sensitive arterial and venous pressures were measured directly, using Statham transducers, and a continuous record before, during, and after cardiac bypass was obtained. By using higher concentrations of CO_2 in the process of oxygenation than are generally recommended, even in the presence of low flow perfusion, arterial hypotension was prevented.

The results of this work suggest that CO_2 is important in the regulation of vascular tone not only in open heart surgery but also in patients with refractory shock.

Venous Drainage of the Septal Artery of the Dog

Thomas W. Moir and Richard W. Eckstein, Cleveland, Ohio

The canine septal artery arising from either the common left or anterior descendens coronary artery was cannulated in 18 dogs with the heart beating in situ. With perfusion of the septal artery through a rotameter from the carotid artery, small volumes (0.05 to 0.5 ml.) of I^{131} serum albumin were injected directly into the cannula tubing, and time-concentration curves

were recorded from sampling sites in the coronary sinus, anterior cardiac veins, and pulmonary artery. By means of standard dilution equations, with flow through these sampling sites known, estimates have been made of the magnitude of septal artery drainage.

With an average septal artery inflow of 56 ml./min./100 Gm. (range 36 to 109), an average of 84 per cent (range 63 to 100) of outflow was accounted for in the pulmonary artery. On the other hand, only an average of 9 per cent (range 2 to 18) was found in the coronary sinus and less than 1 per cent (range 0 to 3) in the anterior cardiac veins.

These data are consistent with direct right ventricular drainage of the majority of septal artery flow. Such drainage of an artery arising from the common left coronary arterial system may explain in part the discrepancy found between common left inflow and coronary sinus outflow and demonstrates that there is direct right ventricular drainage from the coronary vasculature in the beating heart. While such drainage is probably of Thebesian vein character, arterioluminal flow has not been excluded.

Surgical Treatment of Renovascular Hypertension

George C. Morris, Jr., Michael E. De Bakey, Denton A. Cooley, and E. Stanley Crawford, Houston, Texas

Hypertension is one of the most common disorders of man, and its widespread and pernicious effects are well recognized. Revascularization technics which both conserve the kidney and cure hypertension have renewed interest in the surgical treatment of renovascular hypertension, a condition with far higher incidence than previously recognized. In a series of over 80 patients revascularization for renal artery stenosis was carried out, employing either the bypass principle with a graft or direct reconstruction of the narrowed segment of the renal artery with a patch graft. Forty per cent of these patients had bilateral renal artery stenosis and required bilateral renal revascularization. In unilateral renal artery stenosis the kidney distal to the occlusive process becomes the better kidney from both a functional and pathologic point of view after revascularization. Blood pressure in 81 per cent of these patients returned to normal after operation. Nineteen per cent were improved but demonstrated some residual hypertension.

Pulmonary Arteriovenous Fistulas: Physiologic and Clinical Considerations

John H. Moyer and Albert N. Brest, Philadelphia, Pa.

The clinical syndromes produced by pulmonary arteriovenous fistulas are now being recognized with increasing frequency. Extensive roentgenographic examinations of the chest have greatly aided in the diagnosis. Previous misdiagnoses included congenital cyanotic heart disease, primary pulmonary hypertension, polycythemia vera, granulomas, and pulmonary neoplasms. Although the patient may be asymptomatic, the occurrence of clinical symptomatology is primarily related to the interference with normal gaseous exchange. The authors have studied 21 patients with pulmonary arteriovenous fistulas; 3 of the 21 were found in one family with hereditary familial telangiectasia. One patient has been followed for 12 years without operation (and without significant change in the lesion) and another for 12 years after pneumonectomy. Eleven of the 21 had associated vascular abnormalities, occurring most commonly on the skin and mucous membranes. Cardiac catheterization was performed in 10 patients. The pressures in the right heart and pulmonary artery were normal in each; however, the cardiac index was increased in 8 of the 10, and the percentage of cardiac output shunted through the fistulas varied from 3 to 66 per cent. The oxygen saturation ranged from 57 to 94 per cent. The blood volume was increased in 6 of the 10. The most prominent signs were cyanosis, digital clubbing, and epistaxis. Dyspnea on exertion and central nervous symptoms were not infrequent. Surgery was performed in 6 subjects; in each instance good results were obtained with improvement in the physiologic abnormalities.

Study of the Vasodilating Properties of Coumarin Derivatives

Rufus G. Neel, Desmond O'Moore, Eugene G. Wood, and Thos. M. Blake, Jackson, Miss.

The use of coumarin derivatives in the management of symptomatic coronary atherosclerosis is controversial. Convincing proof of consistently adequate suppression of prothrombin activity is rarely included in reports interpreted as showing that patients on such regimens are helped, and some investigators have indicated that such benefit was not attributable to any decrease in the incidence of thromboembolic phenomena. The possibility that these agents act by some means other than interference with coagulation has been suggested, and a few reports have described them as vasodilators but have not included an explanation of the mechanism of this effect. The experiments reported here were designed to study the vasodilating effect of coumarin derivatives, to evaluate this property quantitatively in terms of doses ordinarily used for anticoagulation in humans, and to elucidate its mechanism. Surviving coronary

arteries from swine were perfused with Tyrode's solution at 37 C. in a plethysmographic chamber as described by D. J. Smith. When a baseline was reached, coumarin derivatives were introduced into the perfusate and the change in volume of the specimen recorded.

Fifteen mg. of bishydroxycoumarin injected just proximal to the specimen produced an average maximum dilatation of 0.017 ml. without initial constriction; 12.5 mg. of aminophylline produced an initial constriction of 0.004 ml. followed by a dilatation of 0.005 ml. Reaction to other coumarin derivatives was of the same order. Bishydroxycoumarin added to the perfusate, in a concentration comparable to that found in the serum of patients anticoagulated with it, produced very little response. Vasodilatation produced by coumarin derivatives seems to be a result of a direct drug effect on the arterial wall.

Isolated Ventricular Septal Defect of the Persistent Common Atrioventricular Canal Type

Henry N. Neufeld, Jack L. Titus, James W. DuShane, Howard B. Burchell, and Jesse E. Edwards, Rochester, Minn.

In 9 of 60 necropsy studies and 6 of 300 operated cases of isolated ventricular septal defect, the anatomic defect occupied the same position as the ventricular component of the common atrioventricular canal. Electrocardiographic features were similar in both conditions. In these 15 cases the anatomic defect has been termed "ventricular septal defect of the common atrioventricular canal type."

Deformities of one or both of the atrioventricular valves were noted in 9 of the 15 cases. In no case was an atrial septal defect of the ostium primum type encountered. Serial sections of the main and right bundles revealed that the conduction tissue skirted the posterior and inferior aspects of the defect and, as in common atrioventricular canal, followed an unusually long course because of the low inferior position of the lower edge of the defect.

Electrocardiographic features included a mean QRS axis lying above the isoelectric point (ranging from minus 30 to minus 160 degrees) with the QRS vector in the frontal plane describing a counterclockwise loop with the major portion lying above the zero line. These electrocardiographic findings, while previously considered as strongly supporting the diagnosis of common atrioventricular canal, are shown to occur also in the condition described herein.

Differential Diagnosis of Basal Diastolic Murmurs with the Aid of Cineangiocardiography

A. D. Nichol, F. A. Oldenburg, and H. F. Inderleid, Cleveland, Ohio

Although knowledge of intracardiac anatomic entities, both congenital and acquired, has increased with intracardiac surgery, one of the most perplexing physical findings is the basal diastolic murmur. Until recently basal diastolic murmurs were considered almost pathognomonic of aortic regurgitation or patent ductus with marked shunting. However, entities such as aneurysm of the sinus of Valsalva and anomalous pulmonary valve are characterized by diastolic murmurs at the base of the heart, and clinical interpretation of such murmurs may be difficult.

This is a presentation of several of these anomalies, including an unusual case of agenesis of the pulmonary valve, from the standpoint of clinical findings, electrocardiograms, and catheterization data. However, in each instance the procedure found most helpful was cineangiocardiography.

Surgical Treatment of Mitral Regurgitation Utilizing Extracorporeal Circulation

Henry T. Nichols, Gumersindo Blanco, and Joseph F. Uricchio, Philadelphia, Pa.

The repair of rheumatic mitral regurgitation is best accomplished by an open technic. A more selective annular plication can be done, and more sutures can be inserted with safety. A limited commissurotomy to improve leaflet mobility can be carried out without fear of increasing the regurgitation. Torn or incised leaflets as well as ruptured chordae can be repaired. Valvular debridement is possible.

The mortality rate in the first 50 patients operated on by the open method was 15 per cent. This contrasts favorably with a mortality rate of 27 per cent in 70 patients in whom a closed annuloplasty was used.

Postoperative results have been impressive as shown by the changes in phonocardiograms, chest x-rays, left atrial pressure pulse curve, and cardiac ventriculograms. More recently cineangiocardiography has been employed to evaluate the results of the surgery.

Content of Cephalins in the Plasma of Normal Subjects, Patients with Hyperlipemia and Hypercholesterolemia, and Patients with Coronary Heart Disease

Martin M. Nothman and Samuel Proger, Boston, Mass.

Plasma levels of cephalins, ethanolamine phosphatide, and serine were determined by the method of Axelrod, Reichenthal, and Brodie in normal subjects and in patients with hyperlipemia and hypercholesterolemia and myocardial infarction. These lipids may be important in the clotting mechanism. Ethanolamine phosphatide values ranged between 4.20 and 6.30 mg. per cent and

between 10.12 and 21.20 mg. per cent in 6 normal subjects and 11 patients with myocardial infarctions, respectively. Three patients with hypercholesterolemia but without myocardial infarction had values of 10.72, 14.40, and 19.10 mg. per cent. Values of 16.84 to 28.08 mg. per cent, the highest values in the series, were found in 4 patients who had hyperlipemia, hypercholesterolemia, and xanthomatosis but no myocardial infarction. Serine values ranged from 8.1 to 9.4 mg. per cent, 12.30 to 16.20 mg. per cent, and 15.60 to 26.20 mg. per cent in 4 normal subjects, patients with infarction, and patients with hypercholesterolemia without infarction, respectively. Here again patients with xanthomatosis had the highest values: 28.90 to 36.28 mg. per cent. Cephalin values appear to be related to plasma phospholipid concentrations. Ethanolamine phosphatide normally constitutes 2 to 3 per cent of plasma phospholipids, whereas in the 3 groups above it was 3 to 8 per cent. Serine normally is 4 to 5 per cent of plasma phospholipids; it was 5 to 10 per cent in the 3 groups above. Ingestion of unsaturated fatty acids, which results in a decrease in certain plasma lipid constituents, resulted in a decrease in the cephalins in 5 patients. In 2 patients with xanthomatosis, ethanolamine phosphatide fell from 16.84 to 8.62 mg. per cent and from 28.08 to 10.2 mg. per cent. Serine fell from 28.92 to 14.18 mg. per cent and from 32.16 to 14.60 mg. per cent.

Observations on the Hemodynamic Effects of Isoxsuprine Hydrochloride

Paul Novack, Bernard Goluboff, and Henry A. Shenkin, Philadelphia, Pa.

An ideal peripheral vasodilator should increase peripheral blood flow without reducing blood flow to such vital areas as the brain, heart, or kidneys and without causing a greatly increased cardiac output. The effects of isoxsuprine hydrochloride on cardiac output and cerebral blood flow were observed in a group of 9 patients 30 to 45 minutes after the intramuscular administration of 10 mg. of the drug. The patients ranged from 42 to 81 years of age (average 64 years). Cardiac index averaged 2.76 L./min./M.^{2} prior to and 2.74 L./min./M.^{2} after administration of the drug. Cerebral blood flow diminished by 29 per cent from an average of 56 ml./100 Gm./min. to 40 ml./100 Gm./min. The drop in cerebral blood flow seemed primarily related to a drop in mean arterial pressure from 101 mm. Hg to 84 mm. Hg with a minor increase in cerebral vascular resistance from 2.01 mm. Hg/ml./100 Gm. to 2.15 mm. Hg/ml./100 Gm. Cerebral oxygen consumption remained essentially unchanged, averaging 3.08 ml. O_2/100 Gm./ min. before and 2.95 ml. O_2/100 Gm./min. after the drug. Total peripheral resistance decreased from 1,900 dynes/sec./cm.$^{-5}$ to 1,600 dynes/sec./cm.$^{-5}$. These results indicate that isoxsuprine results in peripheral vasodilatation without an increase in cardiac output. However, the cerebral vessels do not seem to participate in the vasodilatation, and an increased blood flow to other areas is achieved at the expense of a diminished cerebral blood flow. These results apply only to the acute effects of this drug following parenteral administration. Furthermore, the sites receiving an increased fraction of the cardiac output were not defined by this investigation.

Study of Lung Compliance and Surface Tension in Pulmonary Edema

Richard A. Obenour, Herbert A. Saltzman, and Herbert O. Sieker, Durham, N. C.

It has been suggested that the decreased lung compliance found in heart failure may be caused by altered surface tension due to pulmonary edema. Moreover, inhalation of surface-active agents such as alcohol has been reported to relieve symptoms of pulmonary edema. This study was undertaken to assess the relationship of surface tension to compliance in pulmonary edema.

Lung compliance was determined by measuring intrathoracic pressure change with an intraesophageal balloon and lung volume change by measuring alterations in pressure produced by breathing into a 500-L. drum. Observations were made at rest, after maximal inspiration, and following nebulization of surface-active agents in normal subjects and patients with pulmonary edema. The surface tension activity of these agents was determined by measuring their effect on bubble formation by a constant air flow into a mixture of plasma and saline.

Eight studies on normal subjects showed a statistically significant rise in mean compliance from a control value of 0.194 L./cm. to 0.245 L./cm. following alcohol nebulization. A similar rise was noted after alcohol nebulization in some patients with pulmonary edema. Alcohol was shown to decrease surface tension of a plasma-saline mixture in vitro. Conversely, nebulization of a siliconized-superinone mixture, an antifoaming agent, reduced compliance and increased surface tension. These results suggest that the beneficial effects of alcohol inhalation in pulmonary edema may be due to reduced surface tension and the resultant increase in lung compliance. Moreover, these studies indicate that changes in surface tension of pulmonary fluid affect lung compliance.

Adams-Stokes Attacks Resulting from Primary Aldosteronism

Edward S. Orgain, Walter L. Floyd, and Harry T. McPherson, Durham, N. C.

Potassium deficiency in the experimental animal and man can induce necrosis of heart muscle, prolongation of the Q-T interval, and even sudden death.

The usual clinical features of primary aldosteronism, including hypertension and hypokalemic alkalosis, are well known. However, it is not appreciated that an aldosterone-secreting tumor causing potassium deficit may create sufficient cardiac irritability, i.e., prefibrillatory ventricular tachycardia and ventricular fibrillation, to produce recurrent Adams-Stokes attacks characterized by syncope and convulsions.

Therefore, we are reporting the case of a 32-year-old woman who presented the primary complaint of repeated episodes of transient syncope for one month. Examination disclosed a fluctuating hypertension, 140/80 to 240/120, slight cardiac enlargement, but no edema. The electrocardiogram revealed prolonged Q-T interval, premature ventricular beats, transitory prefibrillatory ventricular tachycardia, and ventricular fibrillation. The serum electrolytes were sodium 147 mEq./L., potassium 2.6 mEq./L., chloride 99.8 mEq./L., and CO_2 36.1 mEq./L., while the urine was alkaline. The urinary excretion rates of catechol amines, 17-hydroxycorticoids, and 17-ketosteroids were normal. The patient responded satisfactorily to oral potassium administration. A diagnosis of probable primary aldosteronism was made, and during exploration a tumor was removed from the left adrenal cortex. Aldosterone excretion levels, determined at a later date from urine collected before operation, were elevated 3-fold, proving the correctness of the clinical diagnosis.

Recovery has been complete during the subsequent 2-year period. Blood pressure and serum electrolytes have reverted to normal, and there have been no recurrences of arrhythmia or syncope.

Hemodynamic Effects of Full Phase Negative Pressure Breathing

Hyman W. Paley, James J. Leonard, G. W. N. Eggers, Jr., William J. deGroot, and James V. Warren, Galveston, Texas

The relationship of variations in intrathoracic pressure to central hemodynamics provides an interesting physiologic tool for the study of circulation. Presently available data suggest that effects of negative pressure breathing are reciprocal with those of positive pressure breathing. To assess the effects of negative pressure breathing, 10 healthy male volunteers in the supine position were studied before and at 20 minutes of full phase negative pressure breathing (−20 cm. ± 1 cm. H_2O). Cardiac output and central blood volume were determined by indicator dilution with central injection (radioiodinated serum albumin). Arterial and central venous pressures were recorded and blood oxygen, CO_2, and pH determined just before each indicator injection. On full phase negative pressure breathing, cardiac output increased slightly (0.57 ± 0.17 L./min.; $p<0.0$), heart rate increased (5 ± 2 beats/min.; $p<0.0$), peripheral vascular resistance decreased (−91 ± 83 dynes/sec./cm.$^{-5}$; $p<0.05$), and central venous pressure decreased strikingly (−7.5 ± 1.1 mm. Hg; $p<0.01$). No statistically significant changes occurred in stroke volume, mean arterial pressure, or in blood oxygen, CO_2, or pH. While other reports indicate an increase of thoracic blood volume in response to decreased intrathoracic pressure, central blood volume observed in this study did not increase. It is worthy of note that the observed reactions in this study are not the reciprocal of those in positive pressure breathing. Of particular note is the maintenance of cardiac output in the face of a marked diminution in intrathoracic pressure and central venous pressure during negative pressure breathing. The interrelationship of these effects is of interest in the understanding of circulatory regulation.

Early Manifestations of the Cardiovascular Disorders in Marfan Syndrome

Angelos C. Papaioannou, Magnus H. Agustsson, and Benjamin M. Gasul, Chicago, Ill.

Four children, varying in age from 5 to 26 months, with typical features of Marfan syndrome were studied. Routine clinical and laboratory procedures, phonocardiograms, cardiac catheterizations, peripheral venous and selective angiocardiograms, and retrograde aortograms were performed. The clinical cardiac findings were not significant in any of our 4 patients, consisting of mid and late systolic murmur, accentuated pulmonic component of the second heart sound, and in only one case an apical pansystolic murmur. Cardiac catheterization revealed normal pressures in the right ventricle and pulmonary artery and no evidence of significant mitral or tricuspid regurgitation. Selective angiocardiograms and retrograde aortograms revealed aneurysms of the aortic sinuses of Valsalva, dilatation of the ascending aorta and of the pulmonary trunk, and no evidence of aortic or pulmonic regurgitation. Involvement of the aorta with or without valvular and endocardial lesions in the first 2 years of life in Marfan syndrome has been described previously only at autopsy. In spite of the minimal clinical and conventional laboratory cardiac findings in our cases, contrast radiography demonstrated the presence of serious underlying cardiac lesions. To our knowledge, these are the youngest patients re-

ported in whom the cardiovascular anomalies have been demonstrated during life.

Production of Fibrinolysin Following Administration of Nicotinic Acid to Humans

William B. Parsons, Jr., Madison, Wis.

To study the phenomenon of in vivo production of fibrinolysin following parenteral administration of nicotinic acid in humans, 110 tests have been performed on 53 patients. By means of thrombelastography and direct observation of plasma clots in tubes, fibrinolytic activity was found in 29 of 36 patients (80.5 per cent) after rapid (2 to 5 minutes) intravenous administration of 100 mg. when inhibitory factors were not present. Intramuscular injection (100 mg.) produced fibrinolytic activity in 4 of 9 patients (44 per cent), excluding inhibitory factors, and sublingual or buccal administration (500 mg. nicotinic acid or 250 mg. potassium nicotinate) produced activity in 6 of 8 patients (75 per cent).

The phenomenon was inhibited by daily administration of nicotinic acid or nicotinamide orally in large doses (3 Gm. or more) or by injection of either compound within several hours. The daily use of 50 mg. of nicotinamide in multivitamin products did not cause inhibition. When an attempt was made to reproduce fibrinolytic activity on successive days, the phenomenon usually failed to occur at some time between the second and fifth day, but one patient produced fibrinolysin on 8 successive days.

Neither homologous nor heterologous clots were dissolved by addition of serum showing fibrinolytic activity. Addition of nicotinic acid to blood in vitro failed to result in fibrinolysis.

Studies of nicotinic acid blood levels (by bioassay) and correlation of levels with fibrinolytic activity produced by various routes of administration are in progress, but results are not yet complete.

Clinical Results with Continuously Monitored Extracorporeal Circulation

Bruce C. Paton and Henry Swan, Denver, Colo.

The principles underlying our use of extracorporeal circulation have already been described and the need for monitoring devices emphasized. Nearly 100 perfusions have now been performed using these methods, with detailed physiologic results available from the first 30 cases.

All of the patients were operated on under externally induced hypothermia at 30 C. using a rotating disc oxygenator.

The arterial oxygen tensions, pH, and venous oxygen tensions were continuously monitored. The electroencephalogram, electrocardiogram, and arterial and venous pressures were also monitored in the patient.

A preoperative estimate of oxygen consumption and blood flow was made as an initial guide, but subsequently the A-V O_2 difference and pH were kept within normal limits by adjustments of the pump and disc speeds and oxygenator gas flow rates.

Arterial oxygen tensions were maintained between 85 to 120 mm. Hg and venous tensions between 35 to 45 mm. Hg. The average values for A-V O_2 differences and perfusion rates were 5.3 vols. per cent and 75.4 cc./Kg./min., respectively. Oxygen consumption varied between 1.28 to 13.8 cc./Kg./min., and even at 30 C. the oxygen consumption of children under 10 Kg. exceeded 10 cc./Kg./min. The mean perfusion pressures were between 65 to 120 mm. Hg, and the arterial pH averaged 7.39 before and after perfusion. Bleeding problems were encountered twice, but hemolysis was minimal in spite of long perfusions. The average perfusion time was 50 minutes.

Continuous monitoring of these parameters thus enables physiologic normality to be maintained even during long perfusions.

Physiologic Studies in Patients with Partial Surgical Correction of Transposition of the Great Vessels

Milton H. Paul, Robert A. Miller, and Thomas G. Baffes, Chicago, Ill.

During the past 5 years 117 patients (ages 6 days to 15 years) have had partial correction of transposition of the great vessels by transplanting the inferior vena cava to the left atrium and the right pulmonary veins to the right atrium. Preoperative physiologic studies in 21 patients (16 survived surgery) and pre- and postoperative studies in 8 patients have been analyzed (*a*) to evaluate the hemodynamic consequences of this surgical procedure and (*b*) to provide criteria for the selection of suitable surgical candidates.

The maximum increase in systemic arterial oxygen saturation resulting from surgery was from 39 per cent (preoperatively) to 84 per cent (postoperatively). A large left-to-right atrial shunt was demonstrated in each postoperative study, and calculations indicate as much as a 3-fold increase in pulmonary venous blood entering the aorta after surgery.

The pulmonary artery was entered in 11 preoperative patients. Estimated pulmonary blood flow varied from 1.2 to 3.0 times the systemic blood flow. Pulmonary artery pressure varied from 100/72 to 27/10 mm. Hg. Severe pulmonary artery hypertension per se was not a deterrent to dramatic clinical and physiologic improvement if associated with significantly increased pulmonary blood flow.

Three patients with considerably increased pulmonary vascular resistance (> 10 units) survived surgery with definite but less dramatic improvement. The data also indicate that left ventricular outflow tract stenosis is not a contraindication to this procedure provided the pulmonary blood flow is normal or increased.

Atrioventricular Nodal Tachycardia with Block

Alfred Pick and Richard Langendorf, Chicago, Ill.

Paroxysmal and nonparoxysmal varieties of rapid ectopic rhythms originating in A-V junctional tissues may be associated with various conduction disorders involving transmission of the regular impulses to the atria and/or ventricles, as well as within the ventricles. This is especially true after treatment of the paroxysmal form by digitalis or when A-V nodal impulse formation in a nonparoxysmal form becomes accelerated following digitalis excess. Since retrograde and forward conduction may vary independently or the tachycardia may develop in the presence of atrial fibrillation with A-V dissociation, actual conduction times may not be measurable. The nature of the resulting arrhythmia can be recognized however from the spacing and characteristic grouping of ventricular and/or atrial complexes or from changes in the configuration of ventricular beats, as illustrated by examples of: (*a*) nodal tachycardia with Wenckebach periods of forward conduction and constant retrograde conduction; (*b*) nodal tachycardia with Wenckebach periods of both forward and retrograde conduction; (*c*) nodal tachycardia with progressive retrograde block resulting in reciprocal beating; (*d*) double nodal tachycardias with block causing complete and incomplete A-V dissociation; (*e*) nodal tachycardias with second degree A-V block during atrial fibrillation and complete A-V dissociation; and (*f*) nodal tachycardias with intermittent bidirectional aberration of intraventricular conduction.

Specificity of Plasma Fibrinogen Changes for Atherosclerosis

L. O. Pilgeram, A. C. Schram, and D. Mills, Minneapolis, Minn.

A 34 per cent increase ($p = 0.01$) in the plasma fibrinogen level was found in patients who had recovered from the trauma of a myocardial infarction or a cerebral vascular accident not less than 6 months before and who had not received anticoagulant therapy for at least 5 months preceding the donation of a plasma sample. The interval of time between myocardial infarction or the cerebral vascular accident and analysis indicates (1) that the elevated fibrinogen levels cannot be due to inflammatory conditions or traumatized tissue resulting from the vascular incidents, and (2) that the fibrinogen level does not return to normal following a myocardial infarction or cerebral vascular accident. Occlusion of β- or low-density lipoproteins in the fibrin coagulum did not account for the elevated levels of fibrinogen, as was shown by experiments where (1) known quantities of α- and β-lipoproteins were added to the test system; (2) correction was made for the *occlusion factor;* and (3) the increased yield caused by this occlusion factor represented only a 3.5 per cent increase in fibrinogen yield for as much as a 300 per cent increase in the level of β-lipoproteins.

The data indicate that the fibrinogen level not only increases with age but also superimposes upon the arteriosclerotic an increase in addition to that occurring with increasing chronologic age.

These data support recent reports on the role of fibrin in vascular hypertrophy and atheromatous development. In view of these data, the merit of securing a physiologic homeostasis of fibrinogen metabolism prior to the onset of myocardial infarction or cerebral accidents appears to be unquestionable.

Resection of Coarctation of the Aorta as a Preliminary in Open Heart Surgery

Robert G. Pontius, Pittsburgh, Pa.

This report concerns 2 cases in which coarctation of the aorta was diagnosed and treated as the preliminary portion of a single procedure in open heart surgery.

In an 11-year-old boy with coarctation of the aorta and aortic stenosis, a bilateral anterior thoracotomy was used. Rather large internal mammary arteries were ligated and divided. Because of the sacrifice of these vessels a temporary shunt from the left atrium to the femoral artery was used during the period of aortic occlusion. After the completion of the aortic anastomosis, total body perfusion was instituted, and a direct-vision aortic valvulotomy was carried out.

An 8-year-old girl with a known ventricular septal defect and pulmonary hypertension was also found at repeat catheterization to have a large patent ductus and coarctation of the aorta. Again all lesions were corrected in a single procedure with a preliminary left atrium-to-femoral artery shunt. Total body perfusion was then used for the ventricular septal defect closure.

In addition to the advantages of a single procedure, the avoidance of a second thoracotomy for open heart surgery with the use of anticoagulants in the presence of vascular adhesions would ap-

pe: to be desirable. Both children had uneventful po operative recoveries.

Su gical Correction of the Aberrant Left Pulmonary rtery

obert G. Pontius, Pittsburgh, Pa.

The increasing awareness that an aberrant left pulmonary artery may cause respiratory distress and death in infancy has produced the need for an optimally designed surgical corrective technic. In this anomaly the main pulmonary artery bifurcates at the hilum of the right lung. The aberrant left pulmonary artery arises over the right bronchus and passes posteriorly behind the trachea to the hilum of the left lung. The vascular sling formed may give rise to extrinsic tracheobronchial compression with resulting respiratory difficulties.

Division and reanastomosis of the aberrant left pulmonary artery anterior to the trachea is the logical procedure. During such an anastomosis the entire pulmonary circulation must pass through the right lung. Since partial collapse of the lung is necessary with a right thoracotomy, the time and exposure allowed for such an anastomosis may be limited. Thus an anterior bilateral thoracotomy with division of the sternum is now advised. This procedure was performed in a 5-month-old infant. After the aberrant left pulmonary artery was divided, the proximal end was passed under the superior vena cava and arch of the aorta to rest in an anterior position. An unhurried and precise anastomosis with the distal segment was then carried out. The infant made a prompt and gratifying recovery.

"Stress" and Cardiovascular Disease

Reno R. Porter, Richmond, Va.

In the field of compensation, as well as in rehabilitation and in medicolegal litigation in general, the element of "stress" is being raised more frequently. There is an increasing conviction on the part of many physicians, patients, lawyers, and the public that there is a definite causal relationship between "stress" and cardiovascular disease. This extends beyond circumstances of unusual physical exertion or severe emotional crises to embrace situations encountered commonly in nearly any form of employment. If the present trend continues, one can anticipate the day when all cardiovascular diseases, regardless of the time and circumstances of their manifestations, will be considered compensable. Actual incidences indicate that this is no idle speculation.

Many factors contribute to this situation: (1) a generally held concept that "stress" is bad for the cardiovascular system; (2) the tendency to blame someone else for the misfortunes that befall us, as well as the "bit of larceny" that is present in everyone; (3) reports of investigative studies which in many instances are inadequate and poorly controlled and contain conclusions based as much on speculation as on facts; and (4) the influence of the lay press.

The term "stress" is used freely and with telling effect, but in actuality it is difficult to define and evaluate in any particular individual since it is an entirely personal reaction. Usually efforts to assess its significance are in the realm of imagination and speculation. The time has come to take a more objective look at this current "whipping boy"—"stress"—and to approach the problem with a greater sense of responsibility toward ourselves and toward society as a whole.

Use of Steroids in Heart Block

Myron Prinzmetal and Rexford Kennamer, Los Angeles, Calif.

In 1954 we reported the first use of steroids in the treatment of heart block following an acute myocardial infarction. Subsequently we used the steroids successfully in chronic heart block with Stokes-Adams syndrome. Since that time their value has been confirmed by several other investigators. Sixty cases which were dramatically helped have been analyzed. In many instances the treatment was lifesaving. The present report is an extension of our observations on the use of steroids in heart block and an evaluation of their status in comparison with other accepted therapies. The dosage required may be as high as 100 mg. per day of prednisolone. Conjunctive therapy may consist of chlorothiazide paredrine and sodium chloride. In many cases normal sinus rhythm was re-established. Some of the cases have been successfully treated for 5 years. In several cases the heart block persisted, but there was a dramatic cessation of Stokes-Adams attacks. These observations clearly demonstrate that steroid therapy appears to be firmly established in the treatment of the majority of cases of Stokes-Adams disease. It would seem to be the most practical and effective treatment for ambulatory patients.

Cardiac Arrhythmias Following Intracardiac Surgery

Michael D. Rabbino, New York, N. Y., Leonard S. Dreifus, and William Likoff, Philadelphia, Pa.

Of 211 patients undergoing intracardiac surgery, 39 (19 per cent) patients developed serious postoperative arrhythmias. Auricular fibrillation developed in 10 patients, auricular flutter in 4, and auricular tachycardia in 2. Nonparoxysmal nodal tachycardia with incomplete A-V dissociation was

seen in 9 patients with reciprocal rhythm in 2 and with complete A-V dissociation in 2 others. Ventricular bigeminy occurred in 3 patients with nodal rhythm and a persisent ventricular bigeminy in 6 other patients.

Repair of congenital intracardiac lesions was associated with the highest incidence of serious arrhythmias (33 per cent). On the other hand, there was no apparent difference in the incidence of arrhythmias following mitral as opposed to aortic valvular surgery. However, open procedures carried out with the aid of hypothermia were most frequently associated with serious arrhythmias.

The development of persistent ventricular ectopic beating or complete bundle branch system block associated with a rapid nonparoxysmal nodal tachycardia was a sinister sign; all 5 patients with these mechanisms died. All patients developing rapid auricular mechanisms responded to redigitalization. Invariably patients exhibiting evidence of digitalis excess or insufficient digitalis therapy developed more serious manifestations of these problems. It is important to note that patients who demonstrated auricular premature systoles in the preoperative period usually developed rapid auricular mechanisms postoperatively. Nonparoxysmal nodal tachycardia with incomplete or complete dissociation was usually transient and did not require therapy. Withholding of digitalis in the presence of this rhythm frequently engendered auricular mechanisms. Electrocardiograms taken immediately prior to surgery frequently suggested important clues to the likelihood of serious postoperative arrhythmias.

Cholinergic-like Cardiovascular Effects of Hypertonic Solutions

Raymond C. Read and James Vick, Minneapolis, Minn.

A consideration of the physiologic effects of hypertonic solutions and in particular their vasodilatory and cardiac arrhythmic potentialities suggested that if the sequelae of red cell agglutination were excluded, many of these effects were cholinergic in nature. This hypothesis has been subjected to experimental analysis.

One ml./Kg. of either 12.5 to 50 per cent urea in isotonic saline, 50 per cent glucose, or 5 to 8 per cent NaCl was rapidly injected into the femoral veins of 25 anesthetized dogs. Systemic and pulmonary vascular pressures were monitored and the results compared with those obtained using 1 to 10 μg./Kg. of acetylcholine. Data were collected before and after bilateral cervical vagotomy or treatment with physostigmine (0.5 mg./Kg.) or atropine (1 mg./Kg.).

The results demonstrated a remarkable resemblance between the effects of hyperosmotic media and acetylcholine. In lower concentrations both produced transitory peripheral vasodilatation, while bradycardia and cardiac irregularities became superimposed when stronger solutions were administered. However, changes induced by hypertonic solutions, unlike the cholinergic reactions, were found to be ameliorated by vagotomy, unaffected by atropine, and only partially potentiated by eserine. Vasodilatation which occurred despite denervation also required a latent period of about 10 seconds.

The evidence suggests that hypertonic materials evoke release of acetylcholine as a result of reflex and central nervous excitation. In addition, they exert a direct cholinergic-like action on the cardiovascular system. This finding is consistent with their gastrointestinal, skeletal, and central nervous system effects. A possible mechanism is depolarization of cholinergically innervated effector cells. These observations may be applicable to the problem of angiographic complications.

Hemodynamic and Myocardial Metabolic Response to Cigarette Smoking in Normal and Coronary Subjects

Timothy J. Regan, Jersey City, N. J., Martin J. Frank, John T. McGinty, Detroit, Mich., Harper K. Hellems, Jersey City, N. J., and Richard J. Bing, Detroit, Mich.

The pharmacologic influence of nicotine on myocardial blood flow and oxygen consumption and its possible role in the production of acute myocardial ischemia in man have been evaluated in 2 experimental groups of similar age distribution. Six normal subjects and 8 patients with myocardial infaretion, angina pectoris, and normal heart size were identically studied by the nitrous oxide desaturation technic. After a control determination cigarette smoking was begun and maintained so that the usual systemic pressure and pulse rate increase would persist throughout the redetermination of myocardial blood flow. Associated with the pulse and arterial pressure increase there was a significant rise of left ventricular work in both groups during smoking. In the normals the control myocardial blood flow (83 ± 6 ml./100 Gm. LV/min.) and oxygen consumption (9.4 ± 0.8 ml./100 Gm. LV/min.) were not altered despite the increase in systemic hemodynamic parameters. Consequently the ratio of myocardial O_2 consumption to left ventricular work declined from 1.45 to 1.13 ($p < 0.05$).

The coronary artery disease group had a 30 per cent left ventricular work increment associated with the rate and pressure rise. The resting myocardial blood flow (72 ± 4 ml./100 Gm. LV/min.) and oxygen consumption (8.63 ± 0.5 ml./100 Gm.

L/min.) were lower than in the normals. However, the response to smoking was the same in that there was no flow or oxygen consumption increase. The O_2 consumption-work ratio was similarly reduced from 1.48 to 1.06 ($p < .01$). Despite the susceptibility of this group to myocardial hypoxia the relatively reduced oxygen usage during smoking was not attended by symptoms or electrocardiographic evidence of ischemia. Furthermore, in neither group did the stimulus of pulse rate and arterial pressure increment induce the anticipated increase in myocardial oxygen usage.

Auscultatory and Phonocardiographic Observations in Hyperthyroidism

Norman L. Renfro, James J. Leonard, William J. deGroot, Hyman W. Paley, and Solon L. Coleman, Galveston, Texas

The increased circulatory activity in hyperthyroidism has occasionally led to diagnostic confusion because of the auscultatory findings. To assess this problem, 11 patients with hyperthyroidism were carefully studied by phonocardiography correlated with the hemodynamic alterations. All patients had significantly elevated cardiac outputs, but only one had clinical evidence indicating heart disease. In spite of a short P-R interval (0.14 second average) and a loud first sound, an atrial sound was recorded in 6, either at rest or on returning to the supine position after passive upright tilt. In 7 patients intramuscular reserpine provided a means of slowing the heart rate without a decrease in cardiac output. With the resultant augmentation of diastolic filling, an atrial sound appeared or increased in amplitude if previously recorded. A third (ventricular) heart sound and a basal systolic ejection sound or murmur, probably of pulmonic origin, were observed in 10 patients. Two patients had rumbling diastolic apical murmurs but no other findings indicating mitral stenosis. Splitting of the second sound was prominent in all cases (inspiration 0.05 second average, expiration 0.02 second average). This wide splitting appeared to be related to shortened left ventricular systolic ejection time. A venous hum was audible in the neck in 10 patients and persisted in the supine position in 7. Knowledge of these phenomena not only is of interest in understanding the production of such sounds but also is important in the clinical evaluation of the presence or absence of heart disease in the patient with hyperthyroidism.

Effect on Serum Cholesterol of a Prudent-Type Reducing Diet: Study of 111 Obese Men Fifty to Fifty-Nine Years of Age

Seymour H. Rinzler, Morton Archer, and Norman Jolliffe, New York, N. Y.

Two hundred and seven obese men in the 50-59 year age group were placed on a prudent-type reducing diet: calories about 1,600, protein 140 Gm., carbohydrate 180 Gm., and fat 33.5 Gm. (19 per cent of total calories) with saturated, monounsaturated, and polyunsaturated fatty acids supplying 7.8, 6.5, and 4.7 per cent of total calories, respectively. The addition to this diet of 1½ oz. of corn oil daily plus more fruits and vegetables if required converts it to the prudent diet previously described.

Of the 207 in the starting group, 111 adhered so rigidly to the prescribed diet as to achieve a performance index of 85 or better during the first 10 weeks of observation. Their average control serum cholesterol dropped from 261 to 225 mg. per cent by the end of 6 weeks and remained level thereafter. Of the 111 men, 97 reduced to desirable levels. Seventy-four of these have been maintained on the prudent maintenance diet for at least 6 months, and 56 of these have been maintained for 1 year with the average serum cholesterol remaining level.

The average cholesterol level of the top, middle, and low thirds fell from 307, 251, and 207 mg. per cent, respectively, to 254, 222, and 189 mg. per cent, respectively. Maintenance of weight (after successful weight reduction) by use of the prudent maintenance diet serves to preserve the lowered cholesterol level and prevents its rebound. The lower limit reached by each tertile corresponds very closely to its counterpart in normal weight men with the major point of difference being the earlier fall achieved on the reducing diet.

Evidence for Fractional Contraction of the Normal Heart

Simon Rodbard, Buffalo, N. Y.

The heart is commonly considered to contract on an all-or-none basis; however, there is considerable evidence which may be interpreted as demonstrating that contraction is fractional. Depolarization is all or none, but this is only a permissive condition for contraction. Tension (T) developed in the heart is proportional to the peak product of ventricular pressure (P) and ventricular radius (r) during a given beat. Cardiac oxygen requirements are proportional to tension.

These facts can be explained by considering that the wall tension at onset of mechanical systole triggers a myofibril to contract. This compresses the ventricular contents, increases tension, and triggers other myofibrils to contract in an autocatalytic pattern. The rate of mobilization of tension is thus proportional to the momentary tension. When ejection begins, radius shortens linearly with time, and wall tension is reduced.

The peak tension developed during a normal beat is only a fraction of that which the heart is capable of achieving. The peak tension during a beat determines oxygen uptake: $T = Pr = O_2$. Since each myofibril requires a given amount of energy (oxygen) to re-elongate to the diastolic state, variations in tension development and in oxygen uptake appear to reflect the number of myofibrils triggered in a given beat. The number of myofibrils triggered to contract during a given beat may thus be estimated from data on oxygen uptake and calculations of mechanical tension. These considerations suggest that the normal myocardium contracts in a fractional manner.

Total and Regional Hypothermia with Extracorporeal Circulation

Benson B. Roe and William L. Weirich, San Francisco, Calif.

An improved method for induction of total body or regional hypothermia has been developed which enables the temperature to be controlled easily and simply at any level. The apparatus consists of a single heat exchanger with simple bypass connections. The operator of the pump oxygenator can provide total body or cardiac hypothermia by simply occluding 1 or 2 systems of tubing.

Elective cardiac arrest is accomplished by transaortic or direct coronary perfusion with cold blood at 4 C. Following this type of induced cardiac arrest, the recovery period of the heart is more rapid, and the organ is able to support the circulation more effectively than after comparable periods of potassium-citrate arrest.

This technic may be used when indicated during operations on poor-risk patients with tetralogy of Fallot or acquired valvular disease. Moderate total body hypothermia (27 to 31 C.) has been employed routinely for perfusions lasting more than 45 minutes with considerable benefit to the patient. Deeper levels of total body hypothermia (18 to 21 C.) can be induced to permit total circulatory arrest when the intracardiac operative field is flooded from a persistent surgical (Potts) shunt or a large collateral circulation.

Prognosis and Serum Lipids in Survivors of Myocardial Infarction

Robert D. Roe, Alick Little, and Henry M. Shanoff, Toronto, Canada

Previous studies from this and other centers have shown that patients with coronary heart disease have higher average serum lipid levels than controls. The present report, restricted to the study of survivors of myocardial infarction, examines the relationship between prognosis and the concentration of serum lipids.

Cumulative survival curves were calculated in 120 male patients, aged 30 to 80. They were free of hypertension, secondary hypercholesterolemic states, including diabetes mellitus, and other complicating diseases. The serum lipid fractions determined at the initial examination and annually thereafter included total cholesterol and standard S_f lipoproteins 0-12, 12-20, 20-100, and 100-400.

The over-all 5-year survival from the time of the initial visit was 60 per cent. Each lipid fraction was studied separately. Those men with values above the means for their individual decade were compared with those with values below. The cumulative survival curves in the 2 groups were identical. The results were similar for all lipid fractions studied, whether initial readings only or the means of several readings were used and whether survival was calculated from the first myocardial infarction or from the first examination for this study.

The results indicated that once myocardial infarction occurred, there was no relationship between survival and the concentrations of serum total cholesterol and the standard S_f lipoproteins.

Diagnostic Value of the Ejection Time in Patients with Valvular Heart Disease

Walter H. Roehll, Robert G. Peeler, Durham, N. C., and Arnold M. Weissler, Galveston, Texas

The recent application of technically difficult and sometimes hazardous procedures in the evaluation of patients with heart disease has stimulated a search for simpler but diagnostically precise technics. Therefore, the relationship between left ventricular stroke volume and ejection time in valvular heart disease was investigated. The stroke volume was determined from the cardiac output (indicator dilution or Fick oxygen) and heart rate, while ejection time was derived from the carotid or subclavian pulse tracing (upstroke to base of incisura) obtained externally and recorded at rapid speeds.

In 17 normal resting individuals, in the range of stroke volume from 40 to 110 ml., a linear regression between stroke volume (SV) and ejection time (ET) was observed according to the formula ET (sec.) = .266 + .0017 (SV − 82).

Prolongation of ejection time (greater than 2 SD from the expected value) was found in 18 of 21 patients with aortic insufficiency and in 5 patients with isolated aortic stenosis. When compared to our normal data, prolongation of ejection time was consistently observed in patients with severe isolated aortic stenosis studied by left heart

catheterization (Goldberg et al.). In 9 of 10 patients with surgically demonstrated mitral stenosis or combined mitral stenosis and mitral insufficiency, ejection time fell within normal limits. In 3 patients with both mitral valvular disease and aortic insufficiency, prolongation of ejection time was observed.

The recording of ejection time from the central arteriogram therefore offers a simple, yet accurate adjunct to presently available technics for the detection of hemodynamically significant aortic valvular disease.

Atypical Patent Ductus Arteriosus; Phonocardiographic Criteria Useful in the Differential Diagnosis of This Lesion

William M. Rogers, James R. Malm, James S. Harrison, George H. Humphreys, II, Antonio Demetz, New York, N. Y., and Irwin Simandl, Vienna, Austria

The term "atypical ductus" generally applies to cases in which a continuous murmur cannot be demonstrated. This occurs in extreme pulmonary hypertension. These cases present variable phonocardiographic findings. The consensus of opinion is that the information is diagnostic of pulmonary hypertension but inadequate to establish a patent ductus.

Phonocardiograms and direct pressures before, during, and after occlusion of the ductus have aided in establishing a relationship between the pressures, the direction of the shunt, the velocity of flow in the ductus, the aorta, and the pulmonary artery, and the presence of thrills and murmurs over these vessels.

The significant findings are as follows:

1. An accentuated pulmonary component of the second sound, characteristic of pulmonary hypertension.

2. A systolic murmur over the third and fourth left interspace radiating to the aortic area and the neck is most frequently present. Twenty of our 27 cases were in this group. Direct recordings demonstrated this was an aortic murmur often accompanied by a thrill which disappeared on occlusion of the ductus. Increased velocity through the aortic valve in left-to-right shunts produces this murmur.

3. Often an early diastolic murmur of pulmonary insufficiency is heard over the third left interspace.

4. Occasionally a soft systolic murmur is present over the pulmonary area.

5. Both systolic and diastolic murmurs may be present in the same patient.

In mixed and reversed shunts direct phonocardiograms show no murmur over the aortic valve but a murmur, often a thrill, over the aorta opposite the ductus. This is probably the site of the pumonary systolic murmur.

Precordial Pulsatory Mechanism in Coronary Heart Disease

Leslie M. Rosa and Nevzat Karsak, Chicago, Ill.

The precordial pulsatory mechanism was studied by means of an electromagnetic acceleration pickup. The peak values of acceleration in end-diastole, early systole, end-systole, and early diastole were analyzed in 540 cases.

A series of 296 "coronary" cases (244 patients with clinical and electrocardiographic evidence of coronary heart disease and 52 patients with acute myocardial infarction) was compared with a "control" group of 204 cases (46 normal subjects, 58 patients with essential hypertension without evidence of ischemic heart disease, and 100 patients with underlying diseases other than cardiovascular).

Abnormal end-diastolic pulsatory pattern was found in 22 per cent (45 out of 204 cases) of the control group and in 53 per cent (158 out of 296 cases) of the coronary group. On breakdown, abnormal end-diastolic pulsatory pattern was found in 2 per cent (1 out of 46 cases) of normal subjects; 22 per cent (22 out of 100 cases) of the nonspecific group; 49 per cent (120 out of 244 cases) of the coronary patients; and 73 per cent (38 out of 52 cases) of the infarction group. A similar gradual increase in the occurrence of abnormal pulsatory pattern in other phases of the cardiac cycle was found with progressive evidence of myocardial ischemia or necrosis.

Apart from statistical differences between "ischemic" and "nonischemic" cases, a characteristic deterioration in the pulsatory pattern was found in patients with acute left heart failure (pulmonary edema) with or without electrocardiographic evidence of recent myocardial necrosis.

Right Ventricular Hypertension as a Cause of Angina Pectoris

Richard S. Ross and Benjamin M. Baker, Baltimore, Md.

Chest pain like that of angina pectoris due to coronary atherosclerosis is encountered in young individuals suffering from several circulatory abnormalities associated with high right ventricular pressures. Organic narrowing of the coronary arteries is not present in these patients, and hence there must be a hemodynamic explanation for the chest pain. A positive electrocardiographic exercise test has been recorded from a 19-year-old boy with angina pectoris, patent ductus arteriosus, and pulmonary hypertension. This patient was found

at autopsy to have normal coronary arteries, suggesting that right ventricular myocardial ischemia secondary to elevated right ventricular pressure was responsible for the chest pain.

Cases of angina pectoris in association with congenital heart disease have been collected from hospital records and from the literature. Angina pectoris has been encountered in association with pulmonary stenosis, patent ductus arteriosus with pulmonary hypertension, and in primary pulmonary hypertension. There is right ventricular hypertension in all these conditions, but only in the latter 2 is pulmonary artery pressure also elevated. Right ventricular pressures of the same or greater magnitude are found in the presence of ventricular septal defects in association with either pulmonary stenosis or pulmonary vascular disease, but angina pectoris has not been encountered. Angina pectoris does occur in individuals with right ventricular hypertension and communications between the atria or great vessels. Right ventricular pressure, arterial oxygen saturation, and the electrocardiogram have been recorded during exercise in 2 patients with exertional chest pain and right ventricular hypertension.

Vectorcardiography in the Diagnosis of Abnormal Right Ventricular Hypertrophy in Infants and Children

Edwin L. Rothfeld, Fred W. Wachtel, William S. Karlen, and Arthur Bernstein, Newark, N. J.

Electrocardiographic criteria for abnormal right ventricular hypertrophy in infants and children are based mainly on the height and contour of the R wave or the R/S ratio in right precordial leads. Unfortunately, these criteria are often observed in electrocardiograms of normal infants and children so that considerable difficulty exists in differentiating the normal electrocardiogram from that of abnormal right ventricular hypertrophy in this age group.

In an attempt to resolve this problem, vectorcardiograms, employing the cube reference system, and electrocardiograms were obtained in normal infants and children from birth to 5 years of age. These were compared with vectorcardiograms and electrocardiograms in children with proved right ventricular hypertrophy due to congenital heart disease.

Although the electrocardiograms in the normal subjects were frequently similar to those in children with abnormal right ventricular hypertrophy, a striking difference was observed in the vectorcardiograms. In the normal infant after 3 months of age, the QRS loop in the horizontal plane was oriented to the left and inscribed in a counterclockwise direction. In all cases of abnormal right ventricular hypertrophy, the QRS loop in the horizontal plane was displaced to the right and written in a clockwise direction.

The vectorcardiogram is of value in the diagnosis of abnormal right ventricular hypertrophy in infants and children.

Pulmonary Hypertension in Animals Following Pneumonectomy

Abraham M. Rudolph, Richard J. Golinko, and Peter A. M. Auld, Boston, Mass.*

It has been well established that acute pulmonary hypertension may be induced by resection of major portions of pulmonary tissue. Removal of one lung results in very little acute change in pulmonary arterial pressure, but there is some evidence to suggest that chronic changes in the pulmonary vasculature may be induced.

In order to study the effects of increased blood flow through the remaining lung, left pneumonectomy or surgical occlusion of the left pulmonary artery was performed in dogs. Differences in the effects of these procedures in puppies as compared to adult dogs were studied. Pulmonary arterial pressure measurements and angiograms were performed at intervals for periods up to 18 months.

No acute changes in pulmonary arterial pressure were observed, but within 2 to 4 weeks mean pulmonary arterial pressure had risen from control levels of 7 to 15 mm. Hg to 17 to 28 mm. Hg. After 12 to 18 months the mean pulmonary arterial pressures in the adult animals were 20 to 25 mm. Hg, whereas in the puppies they were 25 to 35 mm. Hg. Pulmonary arteriograms showed the development of progressive dilatation and tortuosity of the pulmonary arteries with a decrease in the peripheral vascular pattern. Histologic examination of the resected and nonresected lungs showed development of medial hypertrophy in the small pulmonary arteries.

These findings suggest that the increased pulmonary blood flow associated with a decrease of the total pulmonary vascular bed may result in vascular obstructive changes in the remaining lung tissue. These changes appear earlier and are more severe in younger animals than in older animals.

Graham Steell Murmur Versus Aortic Regurgitation in Rheumatic Heart Disease: Results of Aortic Valvulography

Vincent Runco, William Molnar, Charles V. Meckstroth, and Joseph M. Ryan, Columbus, Ohio

A major problem in selecting patients for mitral commissurotomy is the accurate evaluation of basal diastolic murmurs. In patients with clinically tight mitral stenosis and evidence of pulmonary hyper-

tension, the murmur is often attributed to relative pulmonic insufficiency if there is no left ventricular enlargement or peripheral manifestation of aortic regurgitation and if right ventricular enlargement is evident from the electrocardiogram or fluoroscopy.

We and others have often found the clinical differentiation between a possible Graham Steell murmur and one of aortic insufficiency to be impossible regardless of the criteria used. Our results with aortic valvulography have substantiated this. In 13 cases with mitral stenosis a basal diastolic murmur was clinically attributed to pulmonic insufficiency. Aortic valvulography subsequently demonstrated aortic regurgitation in 10. In an additional 12 cases, usually complicated by mitral regurgitation, the clinical differentiation between pulmonic and aortic insufficiency could not be made by the usual methods. Of these, 8 showed aortic regurgitation by valvulography.

Our experience would show that aortic insufficiency is probably present in the majority of patients with mitral stenosis diagnosed as having a Graham Steell murmur, and this condition will be overlooked if aortic valvulography is not performed. This unsuspected aortic regurgitation may lessen the chances for anticipated good results following mitral commissurotomy. No reliable method for demonstrating pulmonic insufficiency is available, and although its presence in those patients exhibiting aortic regurgitation cannot be definitely excluded, its true incidence is probably much lower than usually believed.

Isolated Right Ventricular Hypoplasia with Atrial Septal Defect: Occurrence in Three Members of a Family

Marvin A. Sackner, Morton J. Robinson, John Helwig, Jr., Philadelphia, Pa., William L. Jamison, Washington, D. C., and David H. Lewis, Philadelphia, Pa.

With the rare exception of connective tissue replacement of right ventricular myocardium, underdevelopment of the right ventricle as a clinical entity has been related to tricuspid atresia or stenosis, pulmonary atresia, and certain cases of transposition. This report is concerned with 3 members of a family, ages 38, 22, and 12 years, in whom right ventricular hypoplasia and a diminutive chamber were not dependent on these factors. One case was confirmed by necropsy, another by thoracotomy. In association with atrial septal defect, distinctive clinical and hemodynamic features were observed.

These patients were asymptomatic or had mild exertional dyspnea until late in the clinical course when right heart failure supervened. All showed cyanosis, secondary polycythemia, and cardiac enlargement. Systolic murmurs were heard over the sternum in 3 cases, diastolic murmurs in 2 cases. The electrocardiogram showed left axis deviation, left ventricular hypertrophy, and right atrial enlargement. A slight increase in pulmonary vascularity was noted on the chest roentgenogram. Cardiac catheterization demonstrated normal pulmonary artery pressure, no gradient across the tricuspid or pulmonic valves, and a bidirectional atrial shunt. There was a late diastolic plateau in the right ventricle which was approximately one-third systolic pressure. The angiocardiogram showed atrial septal defect and small right ventricle.

This syndrome should be suspected in young adults with intracardiac shunt, right heart failure, and left ventricular hypertrophy. It is confirmed by hemodynamic evidence of atrial septal defect, normal pulmonary artery pressure, no gradient across the tricuspid valve, and restriction to filling of the right ventricle.

Nitrous Oxide Release in Congestive Heart Failure as a Measure of Decreased Blood Flow to Tissues

Herbert A. Saltzman, Walter T. Parkerson, Felice Manfredi,† Samuel J. Friedberg, and Herbert O. Sieker, Durham, N. C.

Slowed circulation and decreased blood flow to certain organs contribute to the pathogenesis of congestive heart failure. While measurements of circulation to single organs have been widely utilized, a method for estimation of body perfusion has not been applied to cardiac decompensation. Since nitrogen elimination rates have been shown to indicate blood flow to various body subdivisions in normal subjects, a modification of this technic using 15 per cent nitrous oxide was tested in 12 edematous heart failure patients before and after anticongestive therapy as well as in 21 normal controls. After patients breathed the test gas, pure oxygen was respired until measurable amounts of nitrous oxide were no longer present in expired air. Turnover rates, which can be equated with blood flow to a unit volume of tissue, were determined for each recorded subdivision of gas elimination.

Twelve heart failure patients demonstrated statistically significant decreases in turnover rates for subdivisions reflecting tissue gas release, with means of 0.17 before and 0.15 after successful diuretic therapy as compared to 0.25 and 0.22 for 11 young and 10 elderly controls, respectively. These observations indicate that heart failure patients eliminate nitrous oxide in an abnormal manner, which is not explained by the aging process or edema fluid retention. It is suggested that

these changes are due to reduced tissue blood flow or to as yet undefined factors. Such tests of inert gas elimination may be useful in studying cardiovascular perfusion abnormalities.

Geographic, Climatic, and Close Residence Effects on Streptococcal Recovery Rates: Relationship to Rheumatic Fever

Milton S. Saslaw, James M. Jablon, Sallie A. Jenks, Margaret Moss, and Madelyn Saul, Miami, Fla.

Because attacks of rheumatic fever are preceded by infection with group A β-hemolytic streptococci, epidemiologic study was done on captive and free children in different cities of Florida to determine (1) geographic (climatic) effects and (2) influence of close residence. Cities selected were Miami (25°46″), Gainesville (29°38″), and St. Augustine (29°54″) the first year and Marianna (30°45″), Ocala (29°15″), and Okeechobee (27°15″) the second. One hundred children were sampled in captive and in free groups in each city. First-year studies were in December 1958-January 1959 and in May 1959; second-year studies in September-October and October-November 1959 and in February and May 1960. In each city the same children were studied at each sampling.

Except for the winter sample in St. Augustine and the September sample in Marianna, all captive groups yielded more β-streptococci than free groups. However, group A recovery rates showed no consistent correlation with freedom or captivity.

Antistreptolysin-O titers were consistently higher in closed groups. Titers were higher when associated with β-streptococcal recovery. Group A organisms were associated with equally high titers in captive and free children. Group C also caused high titers. No seasonal correlations were evident.

Neither rheumatic fever nor glomerulonephritis was observed in any participant during the studies. In Florida, in closed and open groups of children, at different latitudes and in different seasons, on occasion with temperatures below freezing, streptococcal recovery rates and antistreptolysin titers failed to provide any explanation for rheumatic attack rates. Comparison of greater geographic variation is urgently needed; a comparative study between Miami and places which report high rheumatic fever rates is recommended.

Significance of Active Ion Transport Across Large Blood Vessel Walls

Philip N. Sawyer, Ignatius Valmont, Brooklyn, N. Y., David W. Harshaw, Philadelphia, Pa., Harold Steinbaum, and Joel Levine, Brooklyn, N. Y.

Previous studies have shown that disorders of blood flow through both large and small blood vessels may result from induced or spontaneous tissue injury potentials in either the vessel wall or surrounding tissues. The results led to an additional hypothesis that the blood vessel wall must ordinarily expend energy in the active transport of ions to maintain transmural charge at a fixed level (possibly with the intima just negative with respect to both adventitia and the circulating blood) so that blood vessels remain patent.

The flux of Na^{22}, Na^{24}, and Cl^{36} across the membranized oxygenated canine aorta and vena cava in vitro was measured, first, to test the possibility that the blood vessel wall did actively move ions and, second, to measure the rate of ion transport.

Evidence from over 1,000 experiments indicates that active ion transport probably does take place across the large blood vessel wall (aorta, vena cava) in vitro. The energy to carry on the process is apparently provided by both aerobic and anaerobic mechanisms since the loss of O_2 frequently results in a reversal of ion flux across blood vessel walls. It has also been shown that the inner layers of the wall, predominantly the intima and subintimal layers, transport ions at 2 to 10 times the rate of the other layers of the aorta. Additional experiments have been performed at varying temperatures to note temperature dependency of the ion transport mechanism.

The available evidence indicates that the charge across the intimal interface is reversed from negative to positive upon the establishment of anaerobic conditions. It would appear plausible to relate ion fluxes to the maintenance of a P.D. across the blood-intimal interface in order to maintain the ionic equilibrium within the blood and thus prevent coagulation.

Effects of Insulating the Ventricular Surfaces from the Body in Open Chest Electrocardiographic Studies

J. J. Sayen, A. H. Katcher, and G. Peirce, Philadelphia, Pa.

Epicardial and myocardial "unipolar" leads (heart to body surface; direct or capacitor-coupled amplification) were obtained from exposed dog hearts supported by a pericardial cradle with saline-soaked packing beneath it to insure constant posterior mediastinal contact. When a thin sheet of insulation between heart and cradle limited heart-body contact to the vascular pedicle, signals from the ventricular surfaces, walls, or cavities were large (range 20 to 40 mv.). Atrial surface, cavity, and lead II QRS signals were small ($<$ 1 to 2 mv.). Removal of the insulation strikingly lowered all ventricular R waves, increased lead

II amplitude, and reduced to small amplitude the potentials from ventricular surfaces contacting the pericardium.

Application of 50 per cent procaine, 5 per cent KCl, heat, or cold to the epicardium produced localized changes of electrical activity restricted to the ventricular surface and a few millimeters of underlying myocardium. The resultant electrocardiographic changes were confined to the area of application whenever it was isolated from the body (exposure or insulation). When the area was brought into contact with the body, there were widespread reciprocal effects throughout the heart, direct effects in lead II, and attenuation of local signals. Occlusion of medium-sized coronary branches produced electrocardiographic changes limited to the ischemic area but only if its surface was isolated from the body.

The nature and extent of the ventricular surfaces contacting the body grossly alter open chest "unipolar" electrocardiograms. Ventricular surface insulation greatly simplifies "unipolar" lead representations of unevenly distributed electrical changes. "Unipolar" lead study of locally altered ventricular electrical activity requires insulation of the overlying surface.

Five-Year Follow-up Evaluation of Closed Mitral Valvulotomy

J. Gordon Scannell, John D. Turner, John F. Burke, and Farrokh Saidi, Boston Mass.

The application of new technics to operation on the mitral valve makes it imperative to review the long-term results of closed mitral valvulotomy in order to provide a rational basis for open operation as an initial procedure. The authors have studied 100 consecutive patients who survived mitral valvulotomy at the Massachusetts General Hospital between June, 1952 and December, 1954. Follow-up information at 5 years postoperatively has been obtained in the entire consecutive series. Operative results were critically evaluated in terms of rehabilitation and function, and the factors contributing to the success or failure of closed operation were critically examined. Three factors —the sex of the patient, the presence of calcification and extreme deformity of the valve, and finally the inability to perform an adequate valvulotomy in certain cases—appeared to be the chief determinants of a poor result at 5 years. On this basis the authors propose a reasonable approach to open valvulotomy as an initial procedure in the treatment of mitral stenosis to improve the present level of 60 per cent good to excellent results at 5 years.

Change of Serum Lipid Levels with Age: Five-Year Longitudinal Study

Louis E. Schaefer, New York, N. Y., Arthur G. Steinberg, Cleveland, Ohio, David Adlersberg, and Gilberto Ramirez, New York, N. Y.

This investigation involves the re-examination of an ambulatory population 5 years after the first study. Twelve hundred persons in Staten Island, N. Y., from 2 to 72 years of age were originally investigated and average lipid levels computed for 5-year age groups. All available participants in the study are being systematically recalled, and to date approximately one half have been re-examined. It has thus been possible to calculate the actual change with age for several different age groups over a 5-year period.

The actual change with time was always in the same direction and of approximately the same magnitude for all ages in both sexes as the change which had been predicted from the original study. Confirmation of the following predicted trends in serum cholesterol level was obtained: in the female, preadolescent decrease followed by an equivalent postadolescent increase, relative constancy from postadolescence to the mid-30's, and marked increase after age 35; in the male pre- and postadolescent fall and rise of considerably less magnitude than in the female, sharp increase from age 20 to 40, and relative constancy after age 40.

The average change of a group was not demonstrated by all individuals in the group. For example, the average change of 40 preadolescent females was from 210 mg. at age 8 to 193 mg. at age 13, but 11 of the 40 increased rather than decreased. Approximately 35 per cent of individuals in each age group moved in a direction opposite to the general trend. Usually this opposite movement occurred in persons with low levels if the subsequent change for the group was downward and in individuals with high levels if the subsequent group change was upward.

It is possible that the age-change pattern of cholesteremia of an individual will provide a more accurate reflection of the presence or absence of abnormal lipid metabolism than the evaluation of a single lipid value at a given point in time.

Effect of Compounds that Increase or Decrease Amine Activity on the Cardiovascular and Connective Tissue Systems

Arthur L. Scherbel, Cleveland, Ohio

The administration of drugs known to increase or to decrease amine activity influences the manifestations of certain cardiovascular and connective tissue diseases.

Amine oxidase inhibitors release numerous

amines, causing a number of clinical effects. Their action is predominantly central, although peripheral effects occur. Central effects include psychomotor stimulation, sympathetic inhibition, and alteration in certain types of pain. Peripheral effects include stimulation of fibroplasia and spontaneous healing of persistent mesenchymal lesions. The pharmacologic action of numerous unrelated compounds is altered or augmented. Clinical improvement reported to occur in angina pectoris, essential hypertension, and Raynaud's phenomenon is believed to be related to their central action. The healing of mesenchymal ulcers, sinuses, and fistulas complicating inflammatory disease of connective tissue is due to a direct effect on mesenchymal tissue.

Compounds known to inhibit the amines also produce numerous clinical effects. The action of these compounds is predominantly peripheral, but central effects also occur. They inhibit mesenchymal inflammation and fibroblastic proliferation; clinically they alleviate vascular pain and lessen peripheral vasomotor tone. The effect on blood pressure is usually insignificant.

These drugs are useful in the treatment of neuroreflex dystrophy, ischemic ulcers related to Raynaud's phenomenon, and cluster and migraine headaches. They are now being investigated as suppressing agents for mesenchymal inflammatory reactions in allergic conditions and in certain connective tissue diseases.

Anatomic, Clinical, and Hemodynamic Alterations in Thirty-Three Cases of Congenital Corrected Transposition of Great Vessels

Gerold L. Schiebler, Jesse E. Edwards, Howard B. Burchell, James W. DuShane, Patrick A. Ongley, and Earl H. Wood, Rochester, Minn.

Thirty-three cases of congenital corrected transposition of the great vessels are reviewed; 31 patients had normally oriented organs (situs solitus), and 2 patients had situs inversus.

This anomaly, slightly more frequent in males, usually is associated with anomalies of the left atrioventricular valve, a ventricular septal defect, or both. Rarely, it may be an isolated finding.

The diagnosis may be suggested electrocardiographically, particularly with 2:1 or complete atrioventricular block, absent or low-voltage R waves in aV_R, Q waves in V_1, absence of Q waves in V_6, and a clockwise QRS spatial loop in the frontal plane. Thoracic roentgenograms may be helpful, especially when the pulmonary trunk is not clearly delineated in a cardiac contour with a narrow base. An enlarged left atrium with the above features increases the possibility of corrected transposition.

Cardiac catheterization may be diagnostic through careful localization of the atrioventricular and semilunar valves and of the great vessels in anteroposterior and lateral views. Inability to enter the pulmonary artery during right-heart catheterization is common; in these cases selective angiocardiography from the right ventricle can be diagnostic.

The differentiation between ventricular septal defects with corrected transposition and isolated ventricular septal defects is important, since operation in cases with corrected transposition has a tendency to produce atrioventricular dissociation and may reveal a malformed, incompetent left atrioventricular valve not readily repaired.

Effect on Serum Lipid Levels of Corn Oil Versus Pure Oleic and Linoleic Acids in "Atherogenic-Thrombogenic" Diets for Rats

Robert F. Scott, Margaret M. deMaine, and Wilbur A. Thomas, Albany, N. Y.

Various diets inducing "atherosclerosis" and thrombosis in rats have been described. These atherogenic-thrombogenic diets utilize, among other ingredients such as cholesterol and propylthiouracil, different naturally occurring fats to produce high serum lipids. In the current experiment certain pure fatty acids were substituted for natural fat in one of these diets in an attempt to identify specific dietary fatty acids influencing serum lipids.

For 10 per cent corn oil in one type of atherogenic-thrombogenic diet, 10 per cent oleic acid was substituted. In another experiment a 7.5 per cent linoleic-2.5 per cent oleic acid mixture replaced 10 per cent corn oil. Serum cholesterols, lipid phosphorus, and triglycerides were measured in 50 rats.

When 7.5 per cent linoleic-2.5 per cent oleic acid replaced corn oil in the diet, serum lipid levels fell between the "corn oil" group and the "oleic" group. Mean values for "corn oil," "linoleic-oleic," and "oleic" groups were, respectively, cholesterol (expressed as mg. per cent) 1,234, 1,668, and 2,530; lipid phosphorus (as μM per ml.) 6.39, 8.37, and 14.19; triglycerides (as mg. per cent triolein) 476, 531, and 991.

It is perhaps to be expected that substitution of pure oleic acid for corn oil would result in higher serum lipid levels but surprising that increased concentrations of linoleic acid failed to result in lower levels.

Atrial Enlargement in the Diagnosis of Heart Disease

Ronald H. Selvester, L. Julian Haywood, and Donald E. Griggs, Los Angeles, Calif.

The timed vectorcardiogram produces evidence of both right and left atrial enlargement much

earlier than it can be demonstrated by conventional electrocardiographic criteria because of greater amplification of P waves and a more graphic portrayal of their time-phase relationships.

Thirteen-lead electrocardiograms, spatial vectorcardiograms, and timed vectorcardiograms were studied for atrial forces in 100 normals and 304 patients with heart disease (197 congenital, 107 acquired). In all patients the diagnosis was established by cardiac catheterization, surgery, or autopsy. Two separate components of the P wave (an early right and a late left atrial component) could be identified in all but 4 timed vectorcardiograms of the 361 subjects with sinus rhythm.

Of 124 patients with lesions that produce increased right atrial work clinically, 80 per cent (99) showed increased right atrial voltages (beyond 0.05 mv. in the horizontal plane) and anterior and inferior deviation of the early component in their timed vectorcardiograms. Electrocardiograms demonstrated right atrial enlargement in only 12 per cent (15).

Of 137 patients with lesions that produce increased left atrial work clinically, 79 per cent (108) showed increased left atrial voltage (beyond 0.05 mv. in the horizontal plane) and posterior and slightly superior deviation of the late component in their timed vectorcardiograms. Electrocardiograms demonstrated left atrial enlargement in 29 per cent (40).

When P waves were recorded by electrocardiograms taken at 5 times normal amplitude, using orthogonal leads and the above criteria, the clinical correlation closely approximated that of the timed vectorcardiogram. Further study is indicated to see if like criteria can be established when this is done on standard 13-lead electrocardiograms.

Comparative Studies of Acute and Chronic Effects of Digitalis in Cardiac Failure

Arthur Selzer, San Francisco, Calif.

In a group of 15 patients with left ventricular failure in sinus rhythm, the immediate effects of 1.25 mg. of digoxin were studied. The drug was administered when major clinical manifestations of failure were brought under control but failure was evidenced by gross hemodynamic abnormalities. In 10 of the 15 patients digitalis produced marked improvement in cardiac performance by increasing the cardiac output by 35 per cent (average) at rest and 32 per cent during exercise and by lowering left atrial pressure 32 per cent. In the remaining 5 patients digoxin produced no detectable hemodynamic changes. Out of the 10 patients in whom digitalis produced improvement, 5 underwent further study in which the chronic state of digitalization was compared with immediate effects of digoxin. In 3 patients a study of the immediate effects was performed first, then digitalis was maintained at effective or subtoxic levels, and the study was repeated 3 weeks later. In 2 patients hemodynamic assessment of effective chronic digitalization was performed first, and the acute digoxin study was performed 3 weeks after discontinuing digitalis. In all 5 patients the best cardiac performance was observed immediately following administration of digoxin. During the state of chronic digitalization, findings were consistently at intermediate levels between those obtained in the nondigitalized state and those after digoxin. These results suggest that beneficial effects of rapid administration of digoxin may be more pronounced than those maintained permanently in properly digitalized patients.

Right Ventricular Pulse Pressure Wave Patterns: Value in the Etiologic Diagnosis of Right Ventricular Hypertension

Gonzalo D. Sepulveda, Moises B. Brodsky, Luis Bahamondes, and Jorge Ahumada, Santiago, Chile

A study has been made of the value of the right ventricular pulse wave pressure contour in the differential diagnosis of pulmonic stenosis and pulmonary hypertension when the catheter could not be advanced beyond the pulmonic valve. An attempt was also made to differentiate the various types of pulmonary hypertension, namely, those with and without septal or pulmonary defects. A normal pulmonary pressure group (including patients with pulmonary emphysema, congenital lesions with left-to-right shunt, normals, etc.) was used as a control.

Three different patterns were found: (1) the inverted U shape, present in all groups, but mostly in the control (85 per cent); (2) the inverted V shape, also present in all groups, but predominantly in patients with pulmonic stenosis (60 per cent); and (3) the gable type contour, present in almost 70 per cent of the hypertensive group, in none of the controls, and in only 10 per cent of the pulmonic stenosis series.

The normal U-shaped pattern was seldom found in patients with pulmonary hypertension without septal defect (15 per cent), while it was present in nearly 50 per cent of patients with pulmonary hypertension associated with right-to-left shunt.

It is concluded that although the method shows some overlapping, it may be helpful in differential diagnosis.

Diastolic Transmural Pressures and Paradoxic Pulse in Experimental Cardiac Tamponade

Ralph Shabetai,† Noble O. Fowler, and Mosche Gueron, Cincinnati, Ohio

Earlier experimental work showed that negative transmural pressures could be measured from the ventricles when cardiac filling was impeded. In 10 dogs the pleural and pericardial spaces were cannulated, and cannulas were placed in the 4 cardiac chambers and in the aorta and pulmonary artery. The chest was closed, and reversible cardiac tamponade was produced. Measurements of intracardiac and intrapericardial pressures were made. To study pulsus paradoxus, pressures were measured from the pulmonary artery and aorta together with those from the pericardial and pleural spaces.

During cardiac compression negative transmural pressures were seen, first during diastole from the left ventricle and eventually from all chambers. With intrapericardial pressure of 20 mm. Hg, the transmural pressures from all chambers except the left ventricle (in which the transmural systolic pressure was positive) were negative throughout the cardiac cycle. These findings suggest that ventricular suction may develop when cardiac return is impaired by cardiac tamponade.

Intrapericardial pressure of 10 mm. Hg caused a marked increase in the respiratory variation in the systemic and pulmonary arterial pulses. During inspiration the systemic pulse was minimal, whereas the pulmonary arterial pulse was maximal. The respiratory variation in these pulses being opposite in direction suggests that the mechanism of pulsus paradoxus is not dependent on further decreased right heart filling during inspiration. The implication that these pressure changes reflect changes in flow and that during tamponade inspiration increases right ventricular flow and decreases that of the left ventricle awaits confirmation by direct flow measurements.

Fibrin-Intermediates as Indicators of Thrombin Activity in Vivo

John R. Shainoff and Irvine H. Page, Cleveland, Ohio

A cold-precipitable and thrombin-coagulable protein, tentatively designated "cryoprofibrin," was separated from plasma of rabbits treated with *E. coli* endotoxin. It was shown to contain fibrin-intermediates, consisting of fibrinogen that has lost only a portion of the peptides, cofibrins A and B, liberated during the conversion of rabbit fibrinogen to fibrin. On reaction with thrombin, fibrinogen and cryoprofibrin yielded the same amount of cofibrin B (0.9 mole per 220,000 Gm. of fibrin clot); however, cryoprofibrin yielded 30 per cent less cofibrin A than did fibrinogen. Fibrinogen yielded 1.0 mole of cofibrin A per 220,000 Gm. of fibrin. The deficit of cofibrin A in preference to cofibrin B provides evidence that cryoprofibrin consists of fibrinogen that has lost cofibrin A by limited action of thrombin, because cofibrin A is liberated from fibrinogen by thrombin more rapidly than is cofibrin B.

Only a small portion of the cryoprofibrin could have been produced by action of thrombin subsequent to exsanguination, because the plasma contained only about one third of the cofibrin A that had been liberated from fibrinogen during its conversion to cryoprofibrin. Accordingly, cryoprofibrin provides a valid measure of thrombin activity in vivo, at least in endotoxin-treated rabbits.

An average of 0.26 mg. of cryoprofibrin per ml. was obtained from plasma of endotoxin-treated rabbits, as compared with 0.04 mg. per ml. of normal plasma. The demonstration of increased thrombin activity after endotoxin treatment, as shown by the amount of cryoprofibrin, implicates thrombin in the mechanism of fibrinoid deposition.

Susceptibility of Renal Hypertensive Rats to Pyelonephritis and the Predisposition of Pyelonephritic Rats to Hypertension

Alvin P. Shapiro and Jean L. Kobernick, Pittsburgh, Pa.

In previous studies we have demonstrated that (1) rats with experimental chronic pyelonephritis fail to develop hypertensive disease, (2) desoxycorticosterone (DCA) hypertension in rats increases susceptibility to acute pyelonephritis, and (3) infection aggravates DCA hypertension. To clarify further the relationship between pyelonephritis and hypertension, 2 additional experiments have been performed:

1. Forty-three per cent of 30 rats with *renal hypertension* produced by unilateral nephrectomy and clip of contralateral renal artery (mean 158 mm. Hg) developed gross lesions of pyelonephritis 2 weeks after inoculation of *E. coli* without renal massage, in contrast to only 13 per cent of 31 rats with unilateral nephrectomy alone (120 mm. Hg) and 8 per cent of 25 intact controls (113 mm. Hg) ($p = .01$). In a group sacrificed serially, quantitative bacterial counts 24 hours after inoculation were 10 to 100 times higher from the kidneys of hypertensive than from those of normotensive animals.

2. Fifteen rats with chronic pyelonephritis and normal blood pressure were given repeated injections of DCA at widely spaced intervals. After 8 months blood pressure reached 152 ± 19 mm. Hg, while in 15 controls treated with DCA it was 126 ± 19 ($p = .001$). A second group given doses of DCA more rapidly showed blood pressures of 179 ± 14 mm. Hg at 40 weeks; in controls the pressures were 147 ± 27 ($p = .01$).

It thus appears that pyelonephritic rats, although normotensive, are more susceptible to hypertensive stimuli, while rats with hormonal or

renal hypertension are more susceptible to pyelonephritis which may in turn aggravate the hypertensive disease. These several observations taken together could account for the varied clinical aspects of the association between pyelonephritis and hypertension in man.

Effect of Intravenous Fat Emulsions on Human Blood Viscosity

Martin A. Shearn and Aristides Gousios, Oakland, Calif.

The effect of intravenously administered fat emulsion on the viscosity of human blood was investigated because (*a*) hyperlipidemia in animals has been shown to result in increased blood viscosity (Swank) and (*b*) increased blood viscosity has been implicated in the pathogenesis of thrombosis.

Other investigators have employed viscometers with tube lumens smaller than that required for laminar flow. Since major thrombotic episodes in man occur in vessels of medium caliber (coronary or cerebral arteries, femoral vein, etc.), we determined blood viscosity by a simple, reproducible technic that utilized laminar flow, thus more accurately reflecting the situation in medium-sized vessels (Gousios and Shearn). The coefficient of variation as determined by a 2-way analysis of variance on the first 103 determinations was 2 2 per cent.

In 13 hospitalized subjects in the basal state, blood viscosity was determined in triplicate before and after injection of 600 ml. of an emulsion containing 90 Gm. of lipids. All sera became extremely turbid. In some instances the total blood lipid content increased 3-fold after injection of the emulsion. In spite of the magnitude of this rise, blood viscosity showed no significant change.

Treatment of Coronary Insufficiency with Isosorbide Dinitrate

Daniel A. Sherber and Ira J. Gelb, New York, N. Y.

Isosorbide dinitrate (1, 4, 3, 6-dianhydro-sorbitol 2, 5-dinitrate) was shown in laboratory tests to have pharmacologic properties which separate it from other available organic nitrates. In vitro incubation with liver slices showed a rapid uptake of the compound by the liver cell but a slow rate of metabolism, which was confirmed by in vivo animal studies. Isosorbide dinitrate also caused an unequivocal increase in coronary blood flow of the isolated rabbit heart.

On the basis of these studies, it was decided to evaluate this drug clinically in the treatment of coronary insufficiency. This report is a summary of clinical experience with 40 patients, 24 males and 16 females. The duration of treatment ranged from 3 to 19 months. The usual dosage was 10 mg. 4 times daily. The criteria of activity were decreases in the number and severity of anginal attacks. Thirty patients in the group demonstrated almost complete relief of the anginal syndrome with this medication. Ten experienced a considerable degree of freedom from angina, although they occasionally required some sublingual nitroglycerin. Headache was the only complication with this compound but was relieved by reduction in dosage and/or salicylates. All patients except one were relieved of their angina. One patient experienced a recurrence of angina after 5 months of treatment. There was no change in the formed elements of the blood, the blood cholesterol, or blood sugar during the treatment.

Antithrombotic Effects of a Monoamine Oxidase Inhibitor (Hydrazine Derivative)

Takio Shimamoto, Tokyo, Japan

Recently we found that a small amount (0.1 to 1.0 μg./Kg.) of epinephrine produces damage to the "silicone-like property" of blood vessels of rabbits (and men), inducing an abrupt swelling of endothelial cells, appearance of stickiness of these cells to platelets and leukocytes, formation of white thrombi, and at the same time an abrupt decrease in platelet count as well as an abrupt shortening in blood coagulation time. On the other hand, norepinephrine was found to be practically without effect.

Such phenomena were also shown to be produced by oral administration of cholesterol and some fatty substances and by intravenous injection of bacterial polysaccharide.

A monoamine oxidase inhibitor (nialamide) was found to prevent such effects induced by epinephrine, cholesterol, and pyrogenic substances.

The long-term administration to rabbits of 10 mg. of this monoamine oxidase inhibitor daily was found to prevent the appearance of atherosclerosis by cholesterol feeding.

Importance of Free Fatty Acid as Energy Source for Myocardium in Perfused Rat Heart

Joseph C. Shipp, Gainesville, Fla., and Lionel Opie, Boston, Mass.

Studies in vivo by Bing have indicated a significant uptake of fatty acids by the normal myocardium. This report is a study of the uptake of C^{14}-labeled palmitic acid in the isolated rat heart perfused for 30 minutes with a recirculated Krebs-Ringer bicarbonate medium containing 0.5 per cent human albumin and 0.4 mEq./L. of free fatty acid. Uptake of free fatty acid, lactate produc-

tion, residual and labeled heart glycogen, and the amount of label appearing in CO_2 and in tissue fatty acids were measured.

The expected avidity of the myocardium for free fatty acid was evidenced by an uptake of 8.3±0.6 (S.E.) μM./Gm. wet weight/hour; 46±7 per cent of this appeared as CO_2 and 27±5 per cent as tissue fatty acid. None of the label was present in glycogen. Cardiac glycogen decreased by half. Lactate production was adequate to account for about half of the glycogen disappearance. Perfusions with glucose (5 mM.) and free fatty acid (0.4 mEq./L.), each alternately labeled with C^{14}, showed that the uptake of both substrates was unaffected by the presence of the other. However, glucose conversion to CO_2 (20 per cent with glucose alone) was markedly reduced (1 to 2 per cent) when free fatty acid was present. In contrast, the presence of glucose had no effect on the incorporation of C^{14} from palmitate into CO_2.

These observations indicate the important difference between substrate uptake and utilization. They confirm a major role of fatty acid as an energy source for the rat heart and strongly suggest that fatty acid is utilized preferentially when glucose and free fatty acid are present in physiologic concentrations.

Arterial Embolism

H. B. Shumacker and I. Mandelbaum, Indianapolis, Ind.

During a 7-year period, for one reason or another, 21 patients were not treated by direct arterial surgery. Mortality in this group was approximately 20 per cent. Amputation was required, or the affected limbs were ischemic at the time of death in 62 per cent. Amputation was required in two thirds of the 6 cases of embolism to an important artery supplying the upper extremity.

During a 10-year period 81 patients with ischemia of 107 limbs from embolism were treated by direct arterial surgery. Over-all mortality was about 20 per cent. Restoration of adequate circulation was markedly better (80 per cent). There was no relationship between mortality and the site of embolism or the operative procedure required for its correction. Mortality, which was definitely related to the underlying disease which resulted in embolism, was approximately 12 per cent in those with rheumatic heart disease and in those with arteriosclerotic heart disease with or without atrial fibrillation. It was slightly over 50 per cent, however, in patients with recent myocardial infarction.

The survival of limb with adequate circulation was also related to the underlying disease and to the age of the patient. Restoration of good circulation was accomplished in 84 per cent of the cases of rheumatic heart disease but in only about 68 per cent of those with arteriosclerotic heart disease and myocardial infarction. It was possible to restore good circulation in many who were treated one or more days after embolism and in some after an even longer time interval. All the limbs were salvaged when there was no distal propagation of clot beyond the site of the emboli.

Embolism to the aorta and peripheral arteries should with very rare exceptions be treated by direct operative intervention as rapidly as possible after the onset of embolism. There seems little justification for nonsurgical treatment except in cases which are moribund or nearly so at the time of examination.

Surgical Treatment of Patent Ductus Arteriosus

Harris B. Shumacker, Jr., and George Kaiser, Indianapolis, Ind.

Experiences since January, 1949 have been reviewed with the aim of evaluating surgical treatment of patent ductus arteriosus when it occurs as an isolated, uncomplicated lesion, when complicated by infection, recurrence from previous operation, or pulmonary hypertension, and when associated with various other cardiovascular abnormalities. In 220 cases of isolated patent ductus arteriosus, there was no mortality in the typical case without known pulmonary hypertension, endarteritis, or recurrence. One patient with recurrent ductus and endarteritis died shortly after thoracotomy was performed. The other patients with endarteritis or recurrence did well.

Thirty-four patients had mild or moderate pulmonary hypertension. One died postoperatively during bronchoscopy for atelectasis. Thirty-three had hypertension of systemic or near-systemic magnitude. In general, there were difficulties with only one clinical situation: systemic pulmonary hypertension, a small heart showing right ventricular hypertrophy, a large pulmonary trunk, and proximal branch arteries with clear lung fields. With the exception of 4 cases, all the patients did well, including a number with angiographic reversal of flow and one with clubbing of the toes and left hand.

Fifty-four cases had other associated lesions. There was no operative fatality in 21 cases of coarctation and patent ductus, although one patient with the same double lesion ultimately died after initially successful treatment for rupture due to bacterial endarteritis. Fifteen of 19 patients with an associated ventricular defect survived. The 4 patients who died were desperately ill infants. The poorest prognosis was in those patients having a large ventricular septal defect, patent ductus arteriosus, and coarctation. Only one of 7 of these patients has survived.

Controlled Study of Streptococcal Pharyngitis in Children: Factors Related to the Attack Rate of Rheumatic Fever

Allan C. Siegel, Gene H. Stollerman, and Eloise E. Johnson, Chicago, Ill.

The attack rate of rheumatic fever in the general pediatric population following sporadic streptococcal pharyngitis is not known. A controlled study has been in progress during the past 4 years to define the relative risk of giving or withholding antibiotics in the management of pharyngitis in a pediatric clinic population in Chicago. Previous observations indicated a low incidence of rheumatic fever in this group.

Children with pharyngitis and a positive throat culture for β-hemolytic streptococci were divided by random selection into either a benzathine penicillin treatment group or a symptomatically treated control group. Twenty-five hundred children with nasopharyngitis were examined, of which 1,200 (47 per cent) harbored β-hemolytic streptococci. Forty-one per cent harbored group A strains. These 1,200 patients with positive cultures were equally divided into a treated and a control group. Among 600 patients in the control group, there were 2 cases of rheumatic fever (.33 per cent) and 1 case of acute nephritis (.17 per cent). No similar complications occurred in the penicillin-treated group.

In view of the low rheumatic fever attack rate in the control group, the clinical, bacteriologic, and immunologic features of the streptococcal disease encountered were compared to epidemic control groups in a military population which had a rheumatic fever attack rate of 2.8 per cent according to previously published reports. This analysis indicated that the streptococcal disease was considerably milder in the children's group. In only 85 of 600 control patients in the children's group was the illness comparable by clinical, bacteriologic, and immunologic criteria to the infections of the military control group. The attack rate of rheumatic fever in this group of 85 children was 2.8 per cent. The results indicated that the risk of developing rheumatic fever following sporadic nasopharyngitis in a given pediatric population is conditioned by the virulence of the streptococcal disease encountered.

Anticoagulant Therapy in Syndromes of Intermittent Focal Cerebral Arterial Insufficiency: Follow-up and Comparison of Treated and Untreated Cases

Robert G. Siekert, Clark H. Millikan, and Jack P. Whisnant, Rochester, Minn.

During the years 1954-1959 inclusive, a large group of patients with episodes of focal cerebral arterial insufficiency was treated with anticoagulant therapy. These syndromes of vertebral-basilar and carotid arterial system insufficiency, previously described by the authors, consist of episodes of focal cerebral ischemia lasting 15 to 30 minutes with the patient normal between episodes.

The sample to be reported on consists of 103 continuously treated cases and 85 untreated or intermittently treated cases. They have been followed from 1 to 5 years.

Of the patients who received such therapy continuously from the time the diagnosis was established, 85 (83 per cent) remained symptom free; 5 (5 per cent) continued to have attacks without producing cerebral damage, and 7 (7 per cent) suffered a severe stroke, of whom 4 (4 per cent) died, all of cerebral hemorrhage. The remaining died of noncerebral causes.

Of the patients who never received anticoagulant therapy or who received it only briefly, 36 patients (43 per cent) remained asymptomatic; 15 (18 per cent) continued to have attacks without producing cerebral damage, and 30 (36 per cent) suffered a severe stroke, of whom 9 (11 per cent) died, 2 (2 per cent) from intracerebral hemorrhage. The remaining died of noncerebral causes.

These results suggest that anticoagulant therapy has a definite place in the treatment of carefully selected patients with intermittent focal cerebral arterial insufficiency.

Effect of Variations in Cardiac Output and Diastolic Filling Period on the Mitral Diastolic Gradient

Leonard M. Silverman, Philip Samet, William H. Bernstein, Miami Beach, Fla., and Robert S. Litwak, Miami, Fla.

The magnitude of the mitral diastolic gradient varies inversely with the diastolic filling interval in patients with mitral stenosis and atrial fibrillation; the gradient is also a function of the size of the mitral valve and the cardiac output. Since both heart rate and output may be increased during exercise, it is difficult to differentiate between the effects of these 2 parameters on the mitral diastolic gradient during exercise. Such differentiation was attempted in 8 patients with mitral stenosis and atrial fibrillation studied by right and left heart catheterization at rest and during exercise. A beat-by-beat analysis was made of the diastolic gradient and filling interval at rest and during steady-state exercise, and these 2 variables were plotted against each other.

In 7 of the 8 subjects the exercise gradients were larger than the resting gradients at corresponding diastolic intervals. However, considerable variation was observed in the magnitude of the exercise output increment in these 7 patients. These data demonstrate that the elevation in the mitral gradient during exercise is not entirely a

function of the heart rate. It is postulated, therefore, that tachycardia induced by pharmacologic agents such as atropine (unless accompanied by an increase in flow) is not the hemodynamic equivalent of exercise-induced tachycardia.

Age Trends in the Electrocardiogram of "Healthy" Men and Women

Ernst Simonson and Henry W. Blackburn, Minneapolis, Minn.

QRS and T deflections were measured in 12-lead electrocardiograms of 649 healthy men and 311 healthy women, a total of 55,000 measurements. The mean figures in 4 age groups were compared: third decade (115 men, 104 women), fourth decade (110 men, 65 women), fifth decade (214 men, 65 women), and sixth decade (210 men, 77 women). The difference in sample size of sexes was corrected in the statistical treatment. Relative body weight was close to normal (100 per cent) in all groups. There were a greater number of significant electrocardiographic differences with age, 26 in men and 10 in women, and the differences were larger in men than in women. The amplitudes most representative for general QRS and T voltage (lead II, ΣQRS and ΣT for the frontal plane), lead V_2 (largest negative QRS deflection), and V_4 (largest positive QRS deflection for the horizontal plane) decreased with age but more so in men (both absolutely and in percentage of the values for the youngest age group). The differences in the decrease of QRS and T amplitudes between men and women were statistically significant. The finding of more pronounced electrocardiographic age trends in men than women supports the concept that these trends may be related to greater coronary atherosclerotic changes with age in men (established in autopsy material) and to the higher coronary death rate for males. Analysis of electrocardiographic age trends may provide a sensitive index of the prevalence of clinically latent coronary atherosclerosis in populations.

Technic for Taking Down Pott's Anastomosis: Experiences in Three Cases Undergoing Corrective Surgery for Tetralogy of Fallot

Howard D. Sirak and Don M. Hosier, Columbus, Ohio

A patent aorticopulmonary anastomosis previously established for palliation has been a serious obstacle to the definitive open heart correction of tetralogy of Fallot. The location of the anastomotic site and the inevitable postoperative scar involving the great vessels and adjacent structures make the surgical approach through any of the conventional open heart incisions very difficult. Furthermore, the extreme vascularity of adhesions in the left pleural space makes dissection through this area undesirable.

To overcome these inherent difficulties, a new approach has been devised. After the patient has been anesthetized and rendered hypothermic (30 C.) by immersion, the anastomotic area is approached via a small posterior mediastinotomy incision. The hypothermia provides the necessary protection from anoxia in the interval after closing the shunt while preparations are being made for the corrective portion of the operation. After the posterior incision is closed, the patient is turned on his back, reprepped and draped, and a routine open heart correction via a median sternotomy is undertaken. A heat-exchanger in the venous circulation is used to restore the patient's temperature to normal while the repair is being accomplished.

Segmental Replacement of the Superior Vena Cava with Tracheal Homografts

Eugene B. Sive, Callisto Danese, Robert Bower, and John M. Howard, Philadelphia, Pa.

A method has been developed for successful segmental replacement of the superior vena cava by tracheal homografts. Seven dogs out of an initial group of 10 are still alive with patent tracheal homografts for periods of time varying between 2 and 7 months. The patency of the tracheal grafts has been evaluated by serial venograms. Two dogs expired approximately 3 weeks after surgery, and autopsy revealed that a thrombus at the suture line in each instance was the cause of occlusion of each of the grafts. The third dog that died had complete degeneration of the mucosa with occlusion of the tracheal graft. Seventy per cent of the tracheal grafts are currently patent in comparison with the venous homograft series, in which only 4 grafts are open out of an original 17 dogs operated on (24 per cent), and the aortic homograft series, in which only one graft is patent out of an original 11 (9 per cent). All grafts are closed in both the venous homograft (nonsuture coupling technic) series and the plastic prostheses series. A suitable commercial prosthesis incorporating the properties of the trachea seems to lend itself to a more uniformly successful replacement of the superior vena cava.

Hyperlipemia: Types and Differential Diagnosis

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Hyperlipemia may be defined as an elevation of serum triglyceride. This elevation may be primary or secondary to other disease entities such

as diabetes mellitus, nephrotic syndrome, hypothyroidism, or biliary obstruction. The primary and many of the secondary hyperlipemias are due to inability to clear ingested fat from the serum adequately. This inability may be the result of 1 of 2 possible conditions: a total or relative absence of functional lipoprotein lipase, or alternatively, although adequate quantities of the normal enzyme may be present, the mechanism for activating it is deficient. We have been able to differentiate between these 2 causes of hyperlipemia by measuring the response to intravenous heparin. By this method we have established that primary or essential hyperlipemia may be subdivided into at least 2 different disease entities, each due to 1 of the above-mentioned causes.

We have also studied a series of patients with myxedema, all of whom had hyperlipemia and delayed clearing of ingested fat. These patients responded readily to intravenous heparin and therefore had adequate lipoprotein lipase but diminished ability to activate this enzyme spontaneously.

Other diseases causing secondary hyperlipemia are now under study.

Transformation Reactions Among Streptococci

Hutton D. Slade and Dennis Perry, Chicago, Ill.*

Previous investigators have demonstrated the resistance to genetic transformation possessed by the serologic groups of streptococci. No positive results were obtained.

In this investigation, however, it was found that group H streptococci are transformed to streptomycin resistance when subjected to DNA extracts from homologous or heterologous species of streptomycin-resistant streptococci. Certain nontransformable strains were found to act as DNA donors but not as DNA receptors.

A number of strains from groups A, B, C, D, G, H and viridans streptococci were tested. Only group H and certain viridans strains could be transformed to streptomycin resistance.

The number of transformants which occurred depended on the concentration of DNA present. A group A DNA extract was found to be active at a concentration of 10^{-5} μg./ml., while maximum transformation occurred at 10^{-1} to $10^{0}\mu$g. of DNA/ml. The rate of transformation for the strains tested varied from 10^{-10} for a group H strain to 10^{-5} for a viridans strain.

The lack of transformation by certain streptococci may be either physical or genetic. The cell wall or cytoplasmic membrane may be a barrier to the entrance of DNA into the cell. The use of substances known to affect cell permeability did not increase the transformation rate of group H or allow transformation in those negative strains tested.

Experiments are in progress to determine whether this is a genetic phenomenon.

Abnormalities in Blood Coagulation in Patients with Congenital Heart Disease

Sheldon J. Slodki, Irving A. Friedman, Charles L. Pifer, Egbert H. Fell, and Benjamin M. Gasul, Chicago, Ill.

The blood coagulation characteristics of 45 patients with congenital heart disease of varying severity, both cyanotic and noncyanotic types, have been studied. The primary group of tests consisted of bleeding time, tourniquet test, clot retraction, prothrombin time, prothrombin consumption, clotting time, and platelet count. Only one of the patients studied was felt to have chronic hepatic dysfunction secondary to the cardiac lesion. Twenty-four of the patients studied were operative candidates and ultimately had surgical correction of their cardiac lesions. In those patients showing significant abnormalities, additional studies were performed, including thromboplastin generation technics.

The bleeding time was prolonged in 23 patients, most frequently in those with aortic stenosis, coarctation of the aorta, ventricular septal defect, and tetralogy of Fallot. The tourniquet test was slightly positive in only one of the patients with prolonged bleeding time and in none of the others. The clot retraction was found to be impaired in 5 of the patients with prolonged bleeding time and in one patient with a normal bleeding time. The prothrombin time was abnormal in 13 patients and was not consistently associated with a prolonged bleeding time (occurring in only 7 instances). The prothrombin consumption was borderline in only 3 cases, 2 of which had associated prolonged bleeding time. The clotting time was slightly prolonged in only one case and was associated with both poor clot retraction and a prolonged bleeding time. The platelet count was normal in all patients. The prothrombin time abnormalities were never severe (all were found to be just above normal limits). The etiology of the prolonged bleeding time in the absence of other significant coagulation defects in this group of 23 patients is at present unknown. It would appear that a qualitative platelet dysfunction or vascular defect is associated with some forms of congenital cardiac lesions.

Hemodynamic Changes in Man Following Reserpine and l-Norepinephrine

Harold Smulyan, Robert Eich, Richard Cuddy, and Richard Lyons, Syracuse, N. Y.

In order to understand the actions of reserpine, 2 cardiac output measurements by the indicator-dilution technic were done one day apart on each of 31 labile hypertensives. Four hours prior to the second study 14 patients received 2.5 mg. of reserpine intramuscularly, and 17 received saline. Random selection of patients made the groups comparable regarding age, blood pressure, total peripheral resistance (T.P.R.), and pulse. Because 3 cases whose cardiac outputs were over 11 L./min. received reserpine, the mean cardiac output of this group was 0.8 L./min. higher than the controls. Following reserpine blood pressure, cardiac output, T.P.R., and pulse fell, but only the mean blood pressure fall was significant. Two definite responses to reserpine were noted. For those whose T.P.R. was over 1,200 dynes/sec./cm. (11 controls, 8 treated) there was a significant fall in mean blood pressure of 20 mm. Hg and in T.P.R. of 427, compared to controls, but no change in cardiac output or pulse. The remainder, below 1,200, showed a drop in mean blood pressure of 11 mm. Hg secondary to a significant fall in cardiac output of 3.58 L./min. and a *rise* in T.P.R. of 316. Sixteen patients were restudied following a 10-minute infusion of 7.5 μg./min. of *l*-norepinephrine. All patients showed a rise in T.P.R., but there was no difference in the percentage rise between the 9 controls and 7 treated cases.

Intramuscular reserpine therefore lowers the blood pressure by (1) vasodilating if the T.P.R. is elevated and (2) lowering the cardiac output in the presence of vasodilation. It does not appear to inhibit the vasoconstrictor effect of *l*-norepinephrine.

Prognosis of Essential Hypertension Treated Conservatively

Maurice Sokolow and Dorothee Perloff, San Francisco, Calif.

A study was initiated of 617 consecutive patients seen between 1946 and 1953 to determine the 5-year survival of patients with essential hypertension treated by conservative measures. Of these, 51 were lost, and 137 were later excluded because they were found to have secondary hypertension, because potent medical treatment had been given, or because they had subsequent sympathectomy.

The initial status, recorded on IBM cards, included data on sex, age, level of blood pressure, presence and degree of fundal, cardiac (clinical, x-ray, electrocardiogram), renal, and cerebral abnormalities. The 5-year survival was related to these factors individually and in various combinations.

The results on the 439 remaining patients showed that 65 of the 143 men survived 5 years (45 per cent), while 213 of the 296 women (72 per cent) survived 5 years. This decreased survival in men was related in part to the greater severity of their disease on registration. Progressive decrease in yearly survival was found with increments of initial blood pressure, cardiac size (x-ray), degree of left ventricular hypertrophy (electrocardiogram), and fundal changes. Early deaths in patients with good initial status were primarily due to atherosclerosis or noncardiovascular causes. There were a few long survivals among patients with poor initial status.

In conclusion, prognosis may be related to the initial status with the exception of unpredictable atherosclerosis. These data on the survival of patients treated conservatively may be used subsequently for the evaluation of intensive therapy.

Duration of S V_1 as an Index of Left Ventricular Hypertrophy

Louis A. Soloff, Philadelphia, Pa.

It has recently been suggested that the duration of S V_1 can establish the diagnosis of left ventricular hypertrophy. To test this hypothesis, the clinical, radiologic, and electrocardiographic findings in 91 subjects with S V_1 0.06 second or longer were analyzed. Of these 91, 29 had conventional findings of left ventricular hypertrophy. Of these 29, 5 had left bundle-branch block, 5 myocardial infarction, 4 nonspecific electrocardiographic abnormalities, 3 minimal intraventricular conduction delay, and 2 right bundle-branch block. In 4 with myocardial infarction, 5 with nonspecific electrocardiographic abnormalities, one with intraventricular conduction delay, one with pulmonary disease, and 10 with benign hypertension, there was no other evidence to suggest left ventricular hypertrophy, while in 21 there was no other evidence to suggest cardiac disease.

Isolated prolongation of the duration of S V_1 is an unreliable sign of left ventricular hypertrophy.

Electrocardiogram in Subjects with Thick Left Ventricular Walls

Louis A. Soloff, Philadelphia, Pa.

Left ventricular hypertrophy refers specifically to a thick left ventricular wall. Such thickness cannot be measured directly by conventional clinical methods. This term has been regarded in anatomic cardiac literature as synonymous with a heavy heart or a heavy left ventricle. However, if radial spread of ventricular activation takes place, such findings are not the same from the electrocardiographic standpoint. Moreover, left ventricular wall thickness determined in the living subject by the technic of angiocardiography is not

identical with that found at necropsy, and there is no constant relationship between the 2. These differences may partly explain the difficulties in the electrocardiographic diagnosis of left ventricular hypertrophy. Thus, an attempt was made to relate the electrocardiogram to left ventricular wall thickness in living patients. The study was based on 20 consecutive subjects whose angiocardiograms showed thick left ventricular walls. Four had coarctation of the aorta, one congenital aortic stenosis, and the other 15 rheumatic heart disease.

There was no constant relationship between the thickness or degree of thickness of the left ventricular wall and left ventricular activation time, QRS voltage, or T-wave findings. The most consistent findings (but not universal) were increased voltage and T-wave abnormalities. It is suggested that prolonged activation time may be related to decreased electrical velocity rather than increased distance.

Ventricular Premature Beats Diagnostic of Myocardial Disease

Louis A. Soloff, Philadelphia, Pa.

Ventricular premature beats are the most frequent cause of cardiac arrhythmias in man. They occur in otherwise normal hearts as well as in diseased hearts. Their origin and spread of activation are unknown. For these reasons it is generally thought that there is nothing characteristic in a premature ventricular beat which makes it possible to recognize underlying heart disease. One exception is that type of beat which assumes the pattern of myocardial infarction. It is possible, however, that premature beats in their passage through diseased muscle may become diagnostically deformed. To test this hypothesis, the electrocardiograms of 1,000 subjects were reviewed for the presence of ventricular premature beats. The contours of the premature beats were classified and related to the presence or absence of underlying heart disease.

Of 96 subjects with premature beats, 46 had uniform depolarization characterized by slurring which was greatest at onset and by typical secondary T-wave changes. Seventeen occurred in otherwise normal hearts and 29 in diseased hearts.

Fifty had premature beats with bizarre forms of depolarization, repolarization, or both. Depolarization showed irregular slurring and notching. Repolarization simulated coronary changes or deformed S-T segments sharply demarcated from the T wave. Four had Q waves of myocardial infarction. Forty-six of these 50 had other electrocardiographic abnormalities. The other 4 had definite clinical evidence of cardiac disease.

The contour of ventricular premature beats frequently gives clues to the presence of underlying heart disease.

Diagnostic Value of Glyceryl Trinitrate in the Differentiation of Various Cardiovascular Disorders Causing Pulmonary Hypertension

Leonard S. Sommer and Ignatios J. Voudoukis, Miami, Fla.

The effect of sublingual glyceryl trinitrate on pulmonary hypertension was recently studied in patients with left ventricular disease. A pulmonary arterial hypotensive effect was demonstrated in individuals with (1) systemic hypertension associated with left ventricular failure; (2) coronary arteriosclerosis with angina pectoris and/or left ventricular failure; and (3) increased left ventricular work secondary to aortic stenosis insufficiency or mitral insufficiency. This hypotensive response was associated with relief of coexistent anginal pain. Our own studies in patients with these disorders are in accord, and we have extended our observations to individuals with other causes of pulmonary hypertension, namely, mitral stenosis, pulmonary heart disease, and congenital heart disease. Preliminary data suggest that the pulmonary circulation responds to glyceryl trinitrate differently in those with left ventricular failure from those who have pulmonary hypertension without left ventricular failure. Patients with aortic stenosis and cardiac decompensation with or without angina pectoris and those with mitral insufficiency respond with marked reduction in pulmonary artery pressure with no significant systemic hypotension. On the other hand, patients with mitral valve obstruction, primary pulmonary disease, or pulmonary vascular disease associated with congenital cardiac anomalies demonstrate relatively fixed pulmonary hypertension unresponsive to glyceryl trinitrate administration.

Our results lead us to believe that the differential response to nitrates may be useful in the diagnosis of primary cardiovascular disorders resulting in pulmonary hypertension. Studies are now also in progress with a parenteral preparation having nitrate-like properties.

Collateral Arterial Channels in the Living Human with Coronary Artery Disease

F. Mason Sones, Jr., and Earl K. Shirey, Cleveland, Ohio

Cine-coronary-arteriograms, performed by selective opacification of individual coronary arteries, have been used to demonstrate the location and distribution of intercoronary collateral channels in more than 400 patients in whom coronary artery disease was suspected.

There is extreme variation in the development of such channels. In some patients no collateral vessels have been demonstrated 10 months to 3 years after total occlusion of a major artery. In others, such channels are easily demonstrated before complete obstruction of a primary source of flow has occurred. In no instance has intercoronary flow been seen in a patient without clearly demonstrable obstruction in a proximal segment of the vessel receiving the flow.

Following pericardial poudrage, extracoronary collateral channels have not been demonstrated by heavy selective opacification of internal mammary arteries in patients with total occlusion of one coronary artery, even though naturally occurring intercoronary collateral vessels may be seen arising from another partially obstructed vessel.

No reliable objective relationship has been demonstrated between the number and severity of occlusive lesions in major arteries, the presence or absence of collateral channels, and the degree of functional disability caused by angina pectoris.

Frequency of Coronary Thrombi as Related to Duration of Survival from Onset of Acute Fatal Episodes of Myocardial Ischemia

David M. Spain, Brooklyn, N. Y., and Victoria A. Bradess, Valhalla, N. Y.

Over 1,000 consecutive autopsies on sudden or relatively sudden deaths from coronary atherosclerosis with acute myocardial ischemia were analyzed for fresh and recent coronary thrombi. Of these 368 were observed so that the duration of survival from the onset of the acute episode was known. Similarly studied were 200 consecutive autopsies on hospital deaths from acute myocardial infarction patients who had survived at least 24 hours after the onset of the acute episode. The cases were divided into 3 groups: those that had survived less than 1 hour, 1 to 24 hours, and over 24 hours. Fresh or recent coronary thrombi were found in 49 (16 per cent) of 303 cases surviving less than 1 hour, in 24 (37 per cent) of 65 cases surviving 1 to 24 hours, and in 109 (54 per cent) of 200 surviving over 24 hours.

Increased frequency of fresh thrombi accompanied increases in the duration of survival from the onset of the acute episode. These findings would indicate that coronary thrombi may perhaps play only a secondary role in the precipitation of acute myocardial ischemic episodes.

Report on the Treatment of Three Patients with Aortic Insufficiency and Ventricular Septal Defect by Plication of a Prolapsed Aortic Valve Cusp

Frank C. Spencer, Henry T. Bahnson, and Catherine A. Neill, Baltimore, Md.

A new surgical technic has recently been used to correct aortic insufficiency from a prolapsed valve cusp in 3 patients with a ventricular septal defect (ages 8, 9, and 9 years). The insufficiency began at 4 to 6 years of age and progressively increased; the diastolic pressure before operation was 40 mm. Hg or less.

At operation with cardiopulmonary bypass the findings were similar in all 3 patients. The right coronary cusp was greatly enlarged so that it prolapsed downward into the ventricular septal defect, no longer coapting with the other 2 aortic cusps. After the ventricular septal defect was closed through a right ventriculotomy, the aorta was incised to expose the aortic valve. The elongated prolapsed cusp was shortened by "plicating" 12 to 14 mm. of the margin of the cusp with sutures placed through Teflon fabric, after which the cusp coapted with the other 2 cusps. Two surviving patients, one with a grade I diastolic murmur, have diastolic pressures over 70 mm. Hg. Studies with a pulse duplicator of the aortic valve from one patient who died clearly showed the mode of development of the insufficiency and its correction with the plicating sutures.

Incidence of Coronary Artery Disease at Necropsy in a Community of 30,000

Ralph E. Spiekerman, John T. Brandenburg, Richard W. P. Achor, and Jesse E. Edwards, Rochester, Minn.

The high rate of necropsy in deaths among residents of Rochester, Minnesota, provided a unique opportunity to study the prevalence of coronary artery disease and its frequency as a cause of death in the whole community of approximately 30,000. From 1947 through 1952 necropsies were performed after 965 (73 per cent) of 1,326 total resident deaths, including 691 (67 per cent) of 1,026 deaths of persons more than 19 years of age.

Coronary artery disease caused death in 221 patients (23 per cent of all necropsies and 32 per cent of adult necropsies). These 221 (all adults) comprised 40 per cent of men necropsied and 22 per cent of women necropsied. The coronary deaths were attributed to acute coronary failure (sudden death) in 114 (52 per cent), congestive failure in 58 (26 per cent), cardiac rupture in 21 (10 per cent), thromboembolism in 20 (9 per cent), and complications associated with acute myocardial infarction in 8 (4 per cent). An additional 136 patients (20 per cent of the adult necropsies) had significant myocardial necrosis but died of causes other than coronary disease. At least one coronary artery exhibited from 25 to 100 per cent atherosclerotic obstruction in 513 hearts (74 per cent of adult necropsies).

Therefore, among necropsies performed after

two thirds of all deaths in this community, significant coronary artery disease was present in 3 of 4 adults and was the cause of death in 4 of 10 men and 2 of 10 women.

Evidence for Abnormal Blood Coagulation in Sudden Arterial Occlusion

John A. Spittel, Jr., Charles A. Owen, Jr., Charles A. Pascuzzi, and John H. Thompson, Jr., Rochester, Minn.

Sixty-four patients with arteriosclerosis obliterans were investigated by means of a retarded thromboplastin-generation test for the possibility of altered coagulability. A total of 29 of this group demonstrated significant acceleration of the initial steps of coagulation; 26 of these "accelerators" occurred within a group of 40 patients with acute arterial occlusion. Of the 24 patients with chronic arteriosclerosis obliterans but no acute occlusion, only 3 had an exaggerated generation of thromboplastin.

The accelerated coagulation activity was found in patients' adsorbed plasma, but it disappeared with clotting so that serum was normal. The "accelerator" is unaffected by coumarin therapy. However, it is not yet clear whether this abnormal coagulation in patients with sudden arterial occlusion represents the presence of an abnormal clotting factor or of excessive amounts of a normal factor.

The fact that the accelerated thromboplastin generation disappeared within 3 weeks in one patient might suggest that the coagulation defect resulted from the arterial occlusion. In several other patients the acceleration of clotting has persisted as long as it has been studied (3 years in one instance). Perhaps the error in coagulation predisposes to arterial thrombosis; this may contribute to sudden thromboembolic occlusion, which tends to occur in a significant number of persons with arteriosclerosis obliterans.

Hyperuricemia and Hyperglycemia in Acute Myocardial Infarction

Maxwell Spring, Bronx, N. Y., Mehmet Cavusoglu, Yung Ching Chu, and Christina Artymowska, Elmhurst, N. Y.

Hyperglycemia and hyperuricemia can occur in acute myocardial infarction. In this study the incidence and relationship between the two was investigated.

Forty patients with proven myocardial infarction were studied. Six patients died before their studies were completed. Twenty-eight patients completed the entire program, 25 males and 3 females. Age range was 42 to 84 and 50 to 72 years, respectively. None had a history of gout or showed any manifestation of gout. Only 2 were known diabetics. Fasting blood sugars (Folen-Wu), uric acid, and transaminase were performed at weekly intervals. A glucose tolerance test and the steroid modification test using 20 to 25 mg. of prednisone were performed during the fourth week of illness, preceded by preparation with a 300 Gm. carbohydrate diet. A uric acid of 6 mg. or above and a 2-hour blood sugar above 140 mg. per cent were considered abnormal.

Of the 37 who had uric acid determinations performed, 33 patients (89.2 per cent), 27 males and 6 females, exhibited hyperuricemia. The uric acid range was from 6 to 11 mg. per cent. In those patients who survived, the uric acid usually remained elevated during the entire hospital stay.

In the 29 patients who had glucose tolerance tests done, 23 (79.3 per cent), 20 males and 3 females, had an abnormal curve. Ten became positive after the steroid modification.

Of the 28 patients who completed the entire program, 21 (75 per cent), 19 males and 2 females, had both an elevated uric acid and an abnormal glucose tolerance curve.

No correlation was found between the height of the serum transaminase and the level of uric acid. Hyperuricemia was present in every patient with an elevated serum transaminase.

The hyperglycemia and hyperuricemia appear to be related to stress.

Body Weight, Blood Pressure, and Cholesterol in Whites and Negroes and the Problem of Racial Patterns of Coronary Heart Disease

Jeremiah Stamler, Howard A. Lindberg, David M. Berkson, Wilda Miller, Marvin Templeton, and Yolanda Hall, Chicago, Ill.

The problem of comparative rates of occurrence of coronary disease in American whites and Negroes has concerned cardiovascular research for many years. Many contradictory reports are available, some indicating that Negroes have lower coronary disease rates than whites, others indicating similar rates. Our long-term epidemiologic research studies in Chicago living population groups have attempted to focus on this problem. These studies involve approximately 1,600 middle-aged employees of a Chicago utility company, about 100 of them Negro, and approximately 1,600 Negroes from lower income Chicago communities.

For both white and Negro males, similar high prevalence rates for obesity were observed, irrespective of specific socioeconomic background. Mean serum cholesterol levels and prevalence rates of hypercholesterolemia tended to be lower in Negro than white men, particularly in lower income Negroes. Prevalence rates for hypertension and hypertensive heart disease in the utility company population were considerably higher in Ne-

groes than whites. Coronary heart disease prevalence rates were at least as high in these Negro men as in the white men. Data on prevalence of combined abnormalities, including heavy smoking and positive family history, indicate further meaningful relationships between these defects and patterns of occurrence of coronary disease in Negroes and whites. These data illuminate problems of the natural history, pathogenesis, and etiology of atherosclerotic coronary disease in these 2 racial groups in the United States.

Natural History of Pulmonary Hypertension in Children with Ventricular Septal Defects Assessed by Serial Right Heart Catheterization

Robert E. Stanton and Donald C. Fyler, Los Angeles, Calif.

In the past 5 years 23 children with isolated ventricular septal defects have each had 2 cardiac catheterizations in our laboratory. A review of the observed pulmonary artery pressures comprises the basis for this report.

The time interval between procedures averaged 4 years with a range of 2 to 7 years. The mean age at the time of the first procedure was 6.8 years with a range of 1 to 14 years. At the time of the repeat catheterization the mean age was 10.9 years with a range of 5 to 19 years. Thirteen of the 23 children had an initial systolic pulmonary arterial pressure less than 60 mm. Hg, 6 were between 61 and 90 mm. Hg, and 4 were in excess of 90 mm. Hg. The systolic pulmonary arterial pressure in 6 subjects was between 61 and 90 mm. Hg, and in 4 patients it was in excess of 90 mm. Hg.

In none of the 23 children was there a significant increase (over 10 mm. Hg) in pulmonary arterial pressure. The pulmonary arterial pressure decreased in 8 patients. Twenty-one children had a left-to-right shunt, one child had a bidirectional shunt, and one child had a right-to-left shunt. The direction of the intracardiac shunt remained unchanged between procedures.

It appears that the pulmonary arterial pressure in children with ventricular septal defects does not commonly rise with increasing age. This experience correlates well with the observations of the majority of institutions on serially catheterized infants and children with ventricular septal defects.

Evidence for the Production of a Right-to-Left Shunt by Autologous Pulmonary Emboli

Myron Stein, Claude E. Forkner, Jr., Boston, Mass., Eugene D. Robin, Pittsburgh, Pa., George S. Kurland, and Stanford Wessler, Boston, Mass.

Autologous thrombi formed in peripheral veins were released into pulmonary arteries, and the resulting changes in cardiac and pulmonary function were recorded in 35 dogs. Eleven of 14 animals with massive embolization failed to show an increase in arterial oxygen content to control levels following ventilation with 100 per cent oxygen for 20 minutes. Marked decreases in cardiac output, a fall in arterial oxygen saturation during ventilation with room air, and an increase in the arterial-venous oxygen difference without change in oxygen consumption also occurred in these animals. One to 3 hours after embolization the arterial oxygen content returned to control levels after ventilation with 100 per cent oxygen for 20 minutes. In 21 animals in which less extensive obstruction of major pulmonary arteries was observed at necropsy, there were no changes in arterial oxygen saturation, cardiac output, or arterial-venous difference. In both groups, however, pulmonary embolization resulted in an increase in rate, depth, and minute volume of ventilation, a disproportionate increase in dead space ventilation, and an arterial-alveolar CO_2 tension gradient. The only spontaneous death among the 35 dogs occurred in an animal with acute cor pulmonale following massive embolization. The decreased arterial oxygen content while breathing 100 per cent oxygen is consistent with a right-to-left shunt averaging 25 per cent of the total cardiac output. This finding cannot be attributed to "normal" or physiologic shunting alone; its rapid reversal reflects the capacity of the anesthetized animals to compensate for an acute, induced abnormality in pulmonary perfusion.

Technic of Intravenous Carotid and Vertebral Arteriography

Israel Steinberg and John A. Evans, New York, N. Y.

Visualization of the origins of the brachiocephalic arteries has long been possible with the Robb-Steinberg method. A greater bolus effect and, therefore, increased opacification of the cardiovascular system, especially the aorta and its branches, can be achieved by the rapid, bilateral, simultaneous injection of commercially available concentrated organic iodides. With proper positioning of the head and neck and precisely timed roentgenography, the entire course of the carotid and vertebral arteries may be demonstrated from the aortic arch and subclavian arteries to where they pierce the skull.

The erect (anteroposterior or oblique) seated positions with head, neck, and shoulders against roll-film magazine and roentgen tube centered over the neck have proved more satisfactory than the supine position. The time of the roentgen exposure is determined by a modified circulation time test, injecting 3 ml. sodium dehydrochlorate mixed

with 15 cc. normal saline solution through a previously inserted special 12-gage needle-stopcock unit. A single roentgenogram exposed for a second at the time of the bitter taste will show the carotid-vertebral arteries. The best results are obtained when serial exposures at intervals of 2 per second are made 2 seconds before and 2 seconds after the modified circulation time.

Arteriosclerotic buckling, plaques, stenosis, occlusion, and aneurysms of the brachiocephalic arteries were visualized in frontal and oblique views in a series of 31 patients. Although not so vividly portrayed as with direct or retrograde aortic or brachiocephalic artery puncture, the lesions were diagnostic and, of course, only rarely associated with morbidity and fatality.

Total Anomalous Pulmonary Venous Return in Infancy

Aaron M. Stern, Joan M. Sigmann, and Norman S. Talner, Ann Arbor, Mich.

Total anomalous pulmonary venous return when symptomatic in infancy is a grave disease requiring accurate diagnosis for lifesaving surgical correction. Fifteen instances of this condition confirmed at autopsy or surgery have been encountered in children under 2 years. They generally presented with dyspnea and a mild to severe degree of cyanosis.

As a rule physical examination was nonspecific. In addition to cardiomegaly, a systolic murmur of variable intensity along the left sternal border and at times accentuation and splitting of the second sound in the left second interspace were heard. The electrocardiogram was suggestive of right atrial and ventricular hypertrophy.

X-ray examination failed to show the typical figure-of-8 contour among 3 of 5 in this age group with drainage by way of a left superior vena cava. Small, localized indentation of the enlarged coronary sinus into the barium-filled esophagus was seen in 3 cases of pulmonary venous return by this route. Angiocardiography demonstrated the right-to-left atrial shunt in the presence of pulmonary plethora, hypoplastic left and enlarged right heart chambers, and recirculation through the pulmonary circulation. The anomalous return channel was demonstrated as the contrast entered the pulmonary veins.

Cardiac catheterization gave information as to the site of the shunt and the presence of pulmonary hypertension. The right ventricular oxygen saturation, particularly in the patients with anomalous venous return to the coronary sinus, was regularly higher than that of the systemic circulation.

Differences in Cure Rates of Streptococcal Pharyngitis Treated with Two Dosage Schedules of Potassium Penicillin V

Maxwell Stillerman, Stanley H. Bernstein, and Franklin Desposito, New York, N. Y.

A total 494 cases of streptococcal pharyngitis and carrier states were treated initially with potassium penicillin V administered orally in a dose of 125 mg. (200,000 units) or 250 mg. (400,000 units) 3 times daily for 10 days from April, 1956 to April, 1960. Ninety per cent of the patients were under 16 years of age. Beta-hemolytic streptococci were recovered from throat cultures of all patients prior to therapy. Of these, 86 per cent of the known serologic groups were group A. Follow-up cultures in the cured cases were negative 18 to 45 days after commencing therapy at least once in all cases and 2 or more times in two thirds of the cases.

The bacterial cure rate was 78 per cent for 274 cases treated with a daily dose of 375 mg. and 89 per cent for 220 cases treated with a daily dose of 750 mg.

Data on factors in the host, environment, and parasite which might be responsible for the development of relapses were collected.

Our results indicate that (*a*) potassium penicillin V, 250 mg., 3 times daily for 10 days is the dose of choice for the oral treatment of streptococcal pharyngitis and (*b*) 11 per cent of cases will relapse despite this therapeutic regimen.

Direct Studies of the Specialized Conducting System During Hypothermia

Jackson H. Stuckey, Brian F. Hoffman, Albin A. Bagdonas, Juan Piera, and Robert S. Venerose, Brooklyn, N. Y.

By means of a technic developed in this laboratory whereby electrodes may be implanted at specific points within the in situ beating heart, conduction has been studied during hypothermia down to heart temperatures of 7 C. By utilizing cardiopulmonary bypass, electrodes have been placed on the atria, the bundle of His, left or right bundle branches, free-running Purkinje fibers, the Purkinje-papillary junctions, and the ventricular walls. Electrograms from these points, as well as conventional electrocardiograms, were monitored on an 8-channel oscilloscope and photographed at paper speeds of 50 to 200 mm./sec. Heart temperatures were constantly monitored by a thermistor.

Electrical activity at all points monitored disappeared at 7 to 10 C. Appreciable slowing of atrial conduction was apparent when the heart temperature dropped below 36 C.; shifting atrial pacemaker prevented consistent measurement of

atrial conduction time. Conduction velocity in the specialized conduction system at 37 C., measured between electrodes placed on the bundle of His and the right Purkinje-papillary muscle junction, varied from 1.6 to 2.4 M./sec. There appears to be a direct linear relationship between conduction velocity and temperature in the specialized conduction system; during the cooling phase the rate of change in velocity in the specialized conduction system was 0.07 to 0.08 M./sec./degree centigrade. These observations are pertinent to an understanding of some of the aspects of conduction during hypothermia and should be of interest to those employing hypothermia clinically.

Differentiation of the Murmur of Aortic Regurgitation and Pulmonary Regurgitation with Amyl Nitrite

Soon Kyu Suh, Baltimore, Md.

The difference in response of the murmur of aortic regurgitation and pulmonary regurgitation to amyl nitrite inhalation was studied in 23 cases of proved aortic regurgitation and in 13 cases of proved pulmonary regurgitation by means of spectral-phonocardiographic technic.

The diastolic murmur diminished in 21 of 23 cases of aortic regurgitation, including 9 in which it disappeared. In one case a grade 5 murmur was only questionably diminished. In a second patient, who had been taking long-acting nitrite for over 2 months, the murmur did not change. In 3 cases the diastolic murmur increased transiently after the initial diminution (overshoot).

In 11 of 13 cases of pulmonary regurgitation the murmur was either increased or unchanged, including 7 cases with an increase in the diastolic murmur. In 2 cases the phonocardiogram showed questionable diminution. In 6 of 13 cases there was inspiratory accentuation of the diastolic murmur during the postnitrite period. The maximum change in the murmur usually occurred 20 to 50 seconds after inhalation, and intensity returned to the control level usually within 2 minutes.

The Austin Flint murmur diminished. The presystolic murmur, first sound, and opening snap of mitral stenosis were accentuated with amyl nitrite, and there was respiratory variation in the presystolic murmur. The changes of the diastolic murmur were well heard with the stethoscope.

The mechanism of the differential effects of amyl nitrite was studied by cardiac catheterization. The decrease in the aortic diastolic murmur appears to be secondary to the fall in systemic diastolic pressure. The increase in the pulmonary diastolic murmur may be secondary mainly to increased venous return due to hyperpnea produced by amyl nitrite.

Clinicopathologic Study of the Feasibility of Direct Surgical Treatment for Occlusive Coronary Artery Disease

Harry A. Swedlund, Richard W. P. Achor, and Jesse E. Edwards, Rochester, Minn.

The coronary arteries of 112 patients with an antemortem diagnosis of coronary artery disease were studied at necropsy with regard to the feasibility of coronary endarterectomy for direct relief of the luminal narrowing. The size of the main arteries, length of their obstructive lesions, and degree of patency of the small peripheral branches were analyzed. Each heart then was classified as being theoretically eligible for operative correction, susceptible to palliation only, or inoperable. The condition was judged as theoretically operable in 20 cases (18 per cent), as capable of palliation in 58 cases (52 per cent), and as inoperable in 34 cases (30 per cent). Various clinical features (age, sex, angina pectoris, hypertension, diabetes, cardiomegaly, and a history of myocardial infarction) were analyzed in an attempt to find any factors that might suggest a more favorable anatomic state of the coronary arteries in a given patient. No correlation could be discovered in this series. The youngest man judged operable was 54 years of age; of 26 men less than 60 years of age, 2 were considered operable and 12 capable of palliation. Of the 4 women below age 65, none was considered operable, and only 2 were thought to be capable of palliation. In this study it appeared that the more severe and diffuse coronary artery disease was present in the younger male patients. At this time there is little possibility of selecting by clinical means those candidates with occlusive coronary artery disease who might be amenable to direct surgical attack on the arteries.

Postpericardiotomy Syndrome Following Traumatic Hemopericardium

Bernard Tabatznik and James P. Isaacs, Baltimore, Md.

The postpericardiotomy syndrome which follows surgery of rheumatic and congenital heart disease presents as a prolongation of normal postoperative events or as recurrent attacks of chest pain, pyrexia, pericarditis, and pleuritis. A similar syndrome may complicate myocardial infarction and cardiac trauma.

The course of 43 survivors of traumatic hemopericardium was followed. Twenty-seven made a prompt recovery with resolution by the tenth day unless complicated by noncardiac factors (group 1). Five developed an increase in pericardial effusion after an interval of several days but resolved completely within 22 days (group 2)

Eleven (25.6 per cent) ran a prolonged relapse-

ing and remittent course characteristic of postpericardiotomy syndrome (group 3). They showed an active pericardial reaction, manifested by pyrexia, rub, or increasing cardiomegaly at intervals of 6 to 38 weeks after trauma. Two developed generalized intrathoracic polyserositis involving uninjured pleural surfaces. Rapid alterations in heart size independent of therapy were frequent. Patients showing late evidence of "inflow stasis" improved with medical measures. However, chronic constrictive pericarditis necessitating decortication 1½ and 4 years later occurred in 2.

Cardiac tamponade at the time of injury was treated by pericardiocentesis in all group 3 patients. None had open pericardiotomy, in contrast with 8 patients in group 1 and 3 in group 2.

The study draws attention to an increasingly recognized complication of cardiac trauma and confirms the high incidence of postpericardiotomy syndrome in nonrheumatic subjects. Adequate drainage of the hemopericardium may prevent the protracted morbidity of the syndrome and the late development of constrictive pericarditis.

Comparative Study of the Cryptogenic Cardiomyopathies in Africa and in Baltimore, Maryland

Bernard Tabatznik and Richard S. Ross, Baltimore, Md.

A primary myocardial disorder of uncertain etiology which is widespread in the North American Negro is receiving increasing recognition. In Africa the cryptogenic cardiomyopathies are extremely common but show strikingly dissimilar patterns in different areas.

The clinical, laboratory, and pathologic features of the disease in 18 Negro adults in Baltimore were compared with those observed personally in Johannesburg, South Africa. Several similarities were noted. Cardiomegaly with gallop rhythm, a hypodynamic circulation, transient hypertension, and embolic phenomena were frequent findings. A radioisotope scintillation scanning technic was extremely useful in differentiation from pericardial effusion. The Baltimore group comprised 6 who have maintained striking improvement from 1 to 7 years, 4 in chronic congestive failure, and 8 who died after frequent remissions and relapses. The course was similar in the Johannesburg disease. Necropsy changes varied from mild interstitial fibrosis to marked hypertrophy with endocardial thickening and mural thrombosis. The clinicopathologic manifestations differed in several important respects from endomyocardial fibrosis of Uganda.

Laboratory studies helped to exclude acute rheumatic infections, endocrinopathies, liver disease, collagen-vascular disease, and parasitic infections as etiologic agents. Autoimmune antibodies could not be demonstrated by the use of a fluorescein-conjugated antihuman globulin method in 12 Baltimore patients. Nutritional surveys did not suggest malnutrition as a significant factor in the American cardiomyopathy. By contrast, several Johannesburg cases responded dramatically to a ward diet without additional medication. The high incidence of chronic alcoholism in both groups may be of pathogenic importance.

Significance of Atrial Fibrillation and Arterial Embolization in Rheumatic Mitral Valve Disease

Rodman E. Taber and Conrad R. Lam, Detroit, Mich.

A series of 426 mitral commissurotomy patients have been followed from 2½ to 8 years since surgery with particular reference to operative and late mortality as well as functional results. When these patients are considered from the standpoint of presence or absence of atrial fibrillation, certain striking differences are evident. Of 226 patients with normal sinus rhythm at the time of commissurotomy, 65 per cent (145) were regarded as having a good result at the time of the survey, whereas only 42 per cent (83) of those with atrial fibrillation were in this category. The patients with normal sinus rhythm had an operative mortality of 3.3 per cent (8) with 6 per cent (15) late deaths, and the atrial fibrillation group had a 15 per cent (29) operative mortality with 14 per cent (26) late deaths. Of 200 patients with atrial fibrillation, 35 per cent (70) had arterial embolization, 26 per cent (52) preoperatively and 20 per cent (40) postoperatively. Of the 52 patients who had embolism preoperatively, 22 per cent (11) embolized at or following operation with a 64 per cent (7) mortality. The presence of calcification in the valve or clots within the atrium increased the hazard of operative embolization. The significantly increased operative mortality and poorer late results in the patient with atrial fibrillation indicate the need for earlier operation in this group, as well as consideration of open heart surgery in those with previous arterial embolization and in other patients with atrial fibrillation.

Relationship of Rheumatic Fever Recurrence Rate per Streptococcal Infection to Clinical Features in the Patients

Angelo Taranta,† Alvan R. Feinstein, Harrison F. Wood, and Rita Simpson, Irvington-on-Hudson, N. Y.

The attack rate of rheumatic fever after group A streptococcal infections is known to be higher in patients with previous rheumatic attacks than in the general population. In these patients the possible effect of some host factors on the outcome

of streptococcal infections has been analyzed in the present study.

A total of 434 children and adolescents who had had rheumatic fever were examined monthly over a 5-year period for 1,608 patient-years. Monthly throat cultures and at least bimonthly antibody determinations were done. Despite continuous antistreptococcal prophylaxis (sulfadiazine, repository penicillin, or oral penicillin), 267 group A streptococcal infections occurred, which were associated in 44 instances with definite rheumatic recurrences.

Recurrences developed with 16 (9 per cent) of 175 infections in patients with no heart disease and with 28 (30 per cent) of 92 infections in patients with heart disease at the time of the infection. In the latter group 20 infections occurred in patients with markedly enlarged hearts, and 9 (45 per cent) led to rheumatic recurrences. The rheumatic fever recurrence rate per infection likewise increased with the number of previous attacks of rheumatic fever: 10, 23, 27, and 43 per cent in patients with 1, 2, 3, and 4 previous attacks, respectively. This trend was detected despite the increase in age with number of attacks and a decrease of rheumatic fever recurrence rate per infection with age (22, 21, 12, and 8 per cent in the 7 to 9, 10 to 12, 13 to 15, and 16 to 18 age groups, respectively). The recurrence rate per infection also decreased with the time elapsed since the preceding rheumatic attack. It was 24, 16, 11, and 10 per cent in infections which occurred respectively 6 to 23, 24 to 41, 42 to 59, and 60 plus months after the last rheumatic attack.

Contrary to expectation rheumatic fever recurrence rate per infection bore no relationship to the time elapsed since the preceding streptococcal infection.

These data indicate a relationship between the rheumatic fever recurrence rate per infection and certain underlying clinical features which are independent of and antedate the streptococcal infections involved.

Frequency of Overweight, Obesity, Elevated Blood Pressure and Serum Cholesterol in Railroad Clerks and Switchmen

Henry L. Taylor, Ancel Keys, Henry W. Blackburn, Thomas C. Puchner, and Joseph Brozek, Minneapolis, Minn.

Examinations of 1,053 clerks and 833 switchmen between the ages of 40 and 59 were conducted on 32 job sites of 12 railroads operating in the northwestern area of the United States. For analysis the subjects were grouped in 3 major geographic areas, i.e., the plains, the mountains, and the West Coast. Subjects on the plains were further subdivided into 4 groups according to size of the community. For each area and age-quinquennium group, decile values were determined for relative body weight, obesity (skinfold thickness), systolic and diastolic blood pressure, and serum cholesterol. Differences were found between areas in men aged 40 to 49, but not 50 to 59, in skinfolds, relative body weights, and systolic blood pressure. The sum of the skinfolds was least in the mountain area, somewhat larger on the West Coast, and largest in the Chicago-Milwaukee area. Relative body weights and systolic blood pressures followed a similar pattern, but the differences were smaller and disappeared at an earlier age. The distribution of the several variables between switchmen and clerks was tested at the 50th and 80th centile. No differences were found between switchmen and clerks in any of the variables except in Area A, where switchmen contributed an excess of 20 per cent above both 50th and 80th centile in relative body weight. It is concluded that the clerks do not bring to their jobs an undue proportion of the personal characteristics associated with an increased incidence of coronary heart disease.

Death Rates Among Physically Active and Sedentary Employees of the Railway Industry

Henry L. Taylor, Minneapolis, Minn., Ernest Klepetar, St. Paul, Minn., Ancel Keys, Minneapolis, Minn., Willis Parlin, St. Paul, Minn., Henry Blackburn, and Thomas C. Puchner, Minneapolis, Minn.

Clerks, switchmen, and section men were chosen as examples of men whose occupations required physical activity classed as light, moderate, and heavy, respectively. Age, race, years of service in the railroad industry, and social security number were obtained from the Railroad Retirement Board for each male employed in the selected occupations during the calendar year 1954. A cohort was compiled which contained all white males employed in the above occupations who had 10 years of service in 1951 and worked in 1954. Data on deaths were collected from death certificates submitted to the board for death benefit claims for men who had been employed or had held retirement annuities during 1955 and 1956. Deaths were admitted in the study if the social security number could be found in the cohort listing. Death rates for quinquennial age groups between the ages of 40 and 64 were calculated for 1955 and 1956. Age-adjusted death rates for all causes in numbers per 1,000 for both years combined were found to be 11.8 for clerks, 10.2 for switchmen, and 7.6 for section men. Death rates for arteriosclerotic heart disease (numbers 420 and 422) were 5.76 for clerks, 3.87 for switchmen, and 2.79 for section men. As percentage of total deaths, these rates were 48.8 for

clerks, 37.9 for switchmen, and 36.7 for section men. The data are preliminary. The results to date support the concept that less coronary heart disease exists among men holding jobs requiring moderate or heavy physical activity.

Cardiac Output Before and After Induced Pulsus Alternans

Howard K. Thompson, Jr., Julian C. Sleeper, Henry D. McIntosh, Durham, N. C., and Arnold M. Weissler, Galveston, Texas

Despite considerable interest in pulsus alternans, the mechanism remains obscure. A major obstacle to the elucidation of the phenomenon is the inability to produce it consistently in patients without major circulatory alterations. It was fortuitously discovered that marked alteration would be produced in certain recumbent patients 5 to 7 minutes after 1.2 to 2.0 mg. nitroglycerin sublingually. Only those patients who had virtually no alternation during recumbency and who developed almost complete alternans on standing responded to nitroglycerin in this manner.

Seven patients, 6 with myocarditis and one with hypertensive cardiovascular disease, were studied by accepted right heart catheterization technics. Five patients were in overt congestive failure. Cardiac outputs were measured by indicator dilution technics before and after the induction of alternans by nitroglycerin in recumbency. Four patients developed complete alternans, the remaining 3 moderate alternans. No significant change in sinus rate occurred except in one instance where the rate increased from 72 to 96 per minute.

The cardiac outputs before alternans was induced tended to be low (range 2.0 to 5.0 L./min.). The induction of moderate to complete alternans was not accompanied by consistent or striking changes in the output. In one patient the output increased by 0.8 L.; in the others it either did not change or decreased, the greatest decrease being 1.0 L. (25 per cent of control value).

Since in this study pulsus alternans was usually not associated with significant changes in the cardiac output, it would appear that the "strong beats" do indeed eject up to twice the stroke volume as the beats when alternans is not present. These observations suggest that even in profound failure the stroke output may increase, approaching or exceeding normal values. The mechanism producing these changes is not clear.

Preoperative and Postoperative Significance of Peripheral Pulse Pressure Curve Aberrations in Aortic Valvular Disease

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The accurate evaluation of aortic valvular disease is in part dependent on reliable pressure recordings from the left ventricle and systemic circulation. The presence of a harmonic system of standing waves which may alter the shape and magnitude of the peripheral pulse curve has long been recognized. We had underestimated the severity of this standing wave effect. Consequently, we were disturbed to find multiple aberrations in wave form and direct brachial artery pressures which exceeded by 80 mm. Hg or more pressures recorded from the left ventricle. Unless the reasons for this marked alteration are understood, a false impression may be obtained of the severity of aortic insufficiency or stenosis. Furthermore, accurate evaluation of aortic valve operative technics becomes difficult.

In our laboratory the factors responsible for the production of significant standing waves have been studied. In addition, the circumstances under which each plays its role and the magnitude of that role have been analyzed. We have found the following factors to be important: (1) the distance from the heart to the point of measurement; (2) the size of the needle or catheter and its position; (3) the integrity of the system and elasticity of the system's wall (hydraulic ram effect); (4) the cardiac ejection rate; (5) the relationship of the arterial system size to cardiac stroke volume into the aorta; and (6) the size and muscular tone of the peripheral arterial bed.

Effects of Breathing Oxygen-Enriched Mixtures in Various Circulatory States

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The effects of breathing oxygen-enriched mixtures on the hemodynamics and alveolar ventilation were studied in 17 cases. In 6 cases of low output failure breathing 40 per cent oxygen, the cardiac output fell in all cases. In 2 patients not in failure there was little change. In 3 patients with idiopathic hyperkinetic circulatory dynamics, the increased cardiac output at rest fell after they breathed 40 per cent oxygen. Generally little change occurred in pulmonary artery pressures and systemic pressures. In 3 patients with low output failure, breathing 100 per cent oxygen resulted in an appreciable increase of cardiac output in all. The relationship between the cardiac output and the ratios of alveolar ventilation and perfusion was examined in 11 cases. A good correlation existed between the cardiac index and the measured $\dot{V}_A/\dot{Q}_C$ ratio. In general, a low cardiac index was associated with a high $\dot{V}_A/\dot{Q}_C$ ratio, whereas the opposite obtained in patients with high cardiac outputs. When patients breathed oxygen-enriched mixtures, this same pattern was generally followed, although the direction of change varied in individual cases. When cardiac output decreased on

breathing 40 per cent oxygen, there was little change in oxygen consumption but an increase in the A-V difference. This suggests that the tissue demands for oxygen are met at less energy cost to the heart by virtue of the increased oxygen-carrying capacity of the arterial blood. The increased cardiac output on breathing 100 per cent oxygen may result from direct stimulation since total ventilation also increases.

Comparison of Arterenol, Phenylepinephrine, and Epinephrine in Coronary Blood Flow and Ventricular Contractile Force During Cardiopulmonary Bypass

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Direct measurement of coronary blood flow was carried out in 27 open chest dogs during cardiopulmonary bypass using a Mark Kay-Cross type disc oxygenator and pump system. Coronary blood flow was obtained from a cannula placed in the isolated right ventricle, and the Walton-Brodie strain gage arch was used to measure ventricular contractile force. Arteriovenous O_2 differences were determined. Arterenol infusion produced an increase above control levels of approximately 200 per cent in ventricular contractile force, 100 per cent in aortic blood pressure, and 200 per cent in coronary blood flow. Myocardial O_2 consumption increased over 200 per cent and was usually accompanied by a fall in arteriovenous O_2 difference during arterenol infusion. When blood pressure was maintained at control levels by decreasing total body perfusion during drug administration, epinephrine appeared to have the greatest direct dilating effect on the coronary vessels with phenylepinephrine being least effective. Maintaining control blood pressure during drug administration had little effect on ventricular contractile force and heart rate but decreased coronary blood flow approximately 50 per cent. These results indicate that the vasopressor response to these sympathomimetic amines is a major determinant of coronary blood flow. Furthermore, an increase in coronary blood flow greater than is necessary to maintain the usual positive inotropic response to arterenol, with a consequent decrease in efficiency of myocardial O_2 utilization, was indicated by little or no change in ventricular contractile force response following a 50 per cent decrease in coronary blood flow.

Role of the Modern Computer in Analyzing Electrocardiographic Data

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The modern computer is ideal for the quantitation of known diagnostic relations and for the discovery of some relations not determinable by any other means. The goals of the work were as follows:

1. To demonstrate the feasibility of coding electrocardiographic information in a form acceptable to the general purpose computer.

2. To demonstrate the ability of the computer to quantitate statistically those components of the input data which were of the greatest power in separating normal and abnormal tracings.

3. To determine whether computer analysis of these data would result in any additional information not currently available.

The electrocardiographic data analyzed in this project consisted of V_5 tracings from 15 normal subjects and 15 subjects with left ventricular hypertrophy due to aortic insufficiency. The peak amplitudes of P, Q, R, S, T, and S-T, the durations of P, QRS, Q-R, and T, and the intervals of P-Q and Q-T were manually coded and analyzed by the computer according to means, variances, correlation coefficients, and probability density functions.

The analysis revealed significant differences ($p < 0.001$) in 4 means and variances and 9 correlation coefficients between the normal and hypertensive groups. There were 10 means and variances and 12 correlation coefficients significantly different ($p < 0.001$) in the normal and aortic insufficiency groups, indicating a possible use of electrocardiographic data in the etiologic identification of these disease states.

Serum Cholesterol, Lipid Phosphorus, and Atherosclerosis in Chickens: Effect of Diet, Age, Sex, and Sex Hormones

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The relation of specific serum lipids to atherosclerosis was studied in chicks maintained in a replicated experiment for 4, 8, 12, and 16 weeks of age on various nonatherogenic regimens which employed dietary fat and sex hormone administration. By variance analysis significantly higher serum cholesterol was observed in birds fed the more saturated fat diet (tallow) as compared to birds on the more unsaturated fat (corn oil) and control diets. Males had a significantly higher serum cholesterol and atherosclerotic score than females. Diethylstilbestrol in sesame oil, administered at levels of 100 μg./100 Gm. body weight every 3.5 days, significantly elevated serum cholesterol, lowered serum cholesterol-lipid phosphorus ratio, and increased abdominal atherosclerosis. Testosterone proprionate at a dose of 20 μg./.00

(m. body weight every 3.5 days showed no consistent effect.

Spontaneous abdominal atherosclerotic lesions observed in birds as early as 8 weeks of age were augmented by high fat diets and increased in severity as the birds matured.

It is concluded that high serum cholesterol-lipid phosphorus ratios do not necessarily predispose to atherogenesis. Failure to obtain a consistent correlation between serum cholesterol and atherosclerosis among the various regimens would suggest that a mechanism other than or in addition to hypercholesterolemia is involved in the production of the pathology. Local and hormonal factors are implicated.

Intracardiac Prosthetic Valves Using Tissue Culture Membrane Covering

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The practicability of growing an artificial biologic membrane on a suitable cloth base as an aid to fabricating clot-free intracardiac prosthetic valves has been investigated with tissue culture technics, using no foreign protein and growing both homologous and autogenous fibroblasts, canine and human. In the more than 150 cultures and subcultures which have been studied, nylon, dacron, and Teflon were used as base materials, completely eliminating biologic materials other than host blood products.

To date over 50 dogs, prepared by the production of aortic insufficiency, have been used to test coated and uncoated fabric strips in vivo. Unicusp valves placed in the thoracic aorta have remained clot-free up to 9 months.

Placement of unicusp valves in the subcoronary area has been accomplished in specimens and is now being applied to animals, with particular attention to clot prevention and long-term function. Also being investigated is a unicusp valve design for atrioventricular valve replacement.

Effects of Serotonin on Inhibition of the Plasmin-Plasminogen System of the Human

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Recent studies have demonstrated that fibrinolytic activity is produced in local segments of veins by intravenous injection of serotonin. Moreover, the rapidity with which thrombi (artificially induced in rabbit ear veins) are spontaneously lysed depends on their serotonin content. Serotonin inhibits the conversion of fibrinogen to fibrin in purified fibrinogen solutions but accelerates this conversion in the presence of plasma. Since serotonin is a primary amine and several primary amines inhibit thrombolytic activity, it was decided to investigate the in vitro effects of serotonin on fibrinolysis.

An assay system was devised consisting of fibrinogen, thrombin, plasma, imidazole-saline buffer, serotonin, and a commercial preparation of human fibrinolysin. The lysis times were measured. The following substitutions were then made: (1) buffer for serotonin; (2) plasma from a patient with carcinoid disease for normal plasma; (3) buffer for plasma. The effects of incubation of fibrinogen with serotonin and plasmin with serotonin were then determined. The effects of various reactive groups of the serotonin molecule on this system were then evaluated by replacing serotonin with 5-hydroxytryptophane, DL-tryptophane, 3-hydroxytyramine HCl, tyramine free base, and tryptamine HCl.

Carcinoid plasma demonstrated more inhibitory effect on thrombolysis than the control plasma. Serotonin greatly prolonged the lysis time. If the human fibrinolysin was incubated with serotonin prior to the final assay, the lysis times were further prolonged. Serotonin produced the maximum inhibition, followed next by 5-hydroxytryptophane. Tyramine free base was less effective as an inhibitor.

Evidence Against an Extravascular Albumin Space in Edematous Patients

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Two-hour arterial dilution curves of simultaneously administered I^{131}-HSA and Cr^{51}-RBC in 7 edematous patients with heart failure (group 1) and 6 edematous patients with renal disease (group 2) were compared with curves of 7 normal patients (group 3). In all patients the direct plasma volume (I^{131}) was significantly greater than the indirect plasma volume (Cr^{51}) with the first evidence of recirculation. In groups 1 and 3, both isotopes took approximately the same time to complete the period of rapid mixing, and the discrepancy between direct and indirect plasma volume increased at a constant rate, which made the ratio between body and venous hematocrit the same. These data were interpreted to signify that I^{131} did not leave the intravascular space and that the "extra" direct plasma was contained intravascularly in capillaries of lower hematocrit. In patients in group 2, I^{131} took longer than Cr^{51} to complete the period of rapid mixing; red cell mixing at 2 minutes was normal, and the body to venous hematocrit ratio was not constant. These observations suggested that I^{131} escaped the intravascular space. The not excessive direct plasma volume 2 hours after injection argued against extravascular escape of I^{131}

and suggested that the delay in mixing was due to temporarily closed-off capillaries containing only plasma.

Circulatory Adaptations in Hereditary Anemia

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In thalassemia major (Cooley's anemia) severe, lifelong anemia and tissue siderosis are commonly associated with cardiomegaly and venous congestion. The present study was undertaken to elucidate the nature of the cardiovascular disorder in thalassemia major and to distinguish between the roles of the severe anemia and cardiorespiratory siderosis in its production.

Twelve patients, 3 to 27 years old, with Cooley's anemia were studied; 10 had cardiomegaly demonstrated by roentgenogram.

Cardiac output was measured by the direct Fick method for oxygen. Right heart catheterization and arterial cannulation were performed for the sampling of mixed venous and arterial blood and for the measurement of right heart and systemic arterial pressures. Subjects were studied at rest and during exercise both before and after intravenous digoxin, blood transfusion, and the administration of 100 per cent oxygen. Blood volume was measured by T-1824 dilution.

Results show that (1) cardiac output is high at rest, increases inordinately during exercise, and is promptly restored toward normal by transfusion or 100 per cent oxygen; (2) cardiac output, right heart pressure, and heart rate are not affected by acute digitalization; and (3) pulmonary artery pressure and circulating blood volume are normal.

It is concluded that (1) severe anemia rather than cardiorespiratory siderosis is the basis of the cardiovascular disorder in Cooley's anemia; (2) cardiomegaly is an adaptation to increased volume work of the heart rather than myocardial failure; and (3) the circulatory abnormality is improved by transfusion or 100 per cent oxygen rather than by digitalis.

Severe Aortic Stenosis with Pulmonic Stenosis

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Seven children with a combination of aortic stenosis and pulmonic stenosis have been encountered.

Four patients presented with clinical and electrocardiographic picture of aortic stenosis. Pulmonic stenosis was diagnosed during right heart catheterization. There was subvalvular aortic stenosis in all 4. In 2 patients the right ventricular outflow tract obstruction was considered at operation to be due to bulging of a hypertrophied ventricular septum. A third patient had valvular pulmonic stenosis with corrected transposition and a small ventricular septal defect, and in the fourth child the obstruction of the outflow tract was due to protrusion of an aneurysmal right aortic sinus into the right ventricle.

The other 3 patients presented clinical and electrocardiographic evidence of severe pulmonic stenosis. Additional aortic stenosis was suspected on the basis of location and character of the systolic murmur in 2. One patient had a single ventricle, corrected transposition, and infundibular aortic and pulmonic stenosis. The other 2 had combined valvular and infundibular pulmonic stenosis, and the aortic obstruction was valvular in one and subvalvular in the other.

In view of these observations, it is suggested that right heart catheterization be performed in patients with aortic stenosis to determine whether there is accompanying right outflow obstruction. Also the probability of additional aortic stenosis should be considered in individuals with pulmonic stenosis and unusual auscultatory findings.

Effect of Streptococcal Enzymes on Contractility of Human and Guinea Pig Atria

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This study was initiated to determine what effect group A beta-hemolytic streptococcal diphosphopyridine nucleotidase (DPN-ase) and hyaluronidase, as well as the somatic carbohydrate (C substance) obtained from these organisms, would have on the in vitro contractility of normal human and guinea pig myocardia as compared to human and guinea pig myocardia exposed naturally and experimentally to some product of the streptococcus. The experiment was divided into 4 groups: group I—normal guinea pig atria (17); group II—atria obtained from guinea pigs immunized with DNP-ase, hyaluronidase, or control material and considered as "sensitized" (14); group III—right atrial muscle obtained from acyanotic children operated on for congenital heart defects and considered as normal human muscle (10); and group IV—right atrial muscle obtained from adults operated on for correction of rheumatic heart disease and considered as "streptococcal sensitized" human muscle (4).

In group I the control substance alone caused an initial and sustained increase in the height of the contractions. By comparison the DPN-ase and, to a lesser extent, the hyaluronidase caused depression of contractions. The C substance caused

a immediate depression. Sudden, short bursts of s f-limited spontaneous activity developed in 47 p cent (8 of 17) of normal atria.

In group II the increase in height of contractions in all groups suggested a nonspecific response to some other constituent in the preparation. A second group of guinea pigs, immunized with a dinitrophenol bovine gamma globulin antigen, was studied. On addition of the antigen to the sensitized atrium, a similar pattern of sudden onset of spontaneous activity and increase in height of contraction was uniformly elicited. In the combined groups, 91 per cent (21 of 23) exhibited onset of spontaneous activity.

In Groups III and IV, DPN-ase, hyaluronidase, and the control had no effect on the height of contraction of either group. The pattern of inherent rhythmicity was altered. The C substance caused an immediate depression of short duration in 86 per cent (6 of 7) of the normal human atria and 100 per cent (5 of 5) of the "sensitized" human atria.

Under the conditions of the experiments, streptococcal DPN-ase appeared to depress guinea pig atrial contractions; this effect could not be demonstrated in either group of human atria. The C substance, as prepared, depressed both guinea pig and human atria, severely in the former and transiently in the latter. The response of the immunized guinea pig atria to the sensitizing antigen under these conditions is one of increased height of contraction and development of irregular, spontaneous rhythm; the atria from these animals were more irritable than the normals handled in the same manner.

Hemodynamic Studies Before and After Iatrogenic Hypothyroidism in the Treatment of Severe Heart Failure

John H. K. Vogel and Joseph M. Merrill, Nashville, Tenn.

Iatrogenic hypothyroidism as a treatment for severe heart failure is frequently associated with significant symptomatic improvement. However, actual correlation of hemodynamic studies with symptomatic changes before and after treatment are rare. The purpose of this paper is to report the effects of radioactive iodine and methimazole on hemodynamic functions and symptomatology in 4 patients with severe heart failure, 3 associated with rheumatic heart disease and one with emphysema.

Following treatment and associated with the onset of clinical and laboratory findings of hypothyroidism, all patients noted symptomatic improvement characterized by decrease in dyspnea, orthopnea, and fluid retention with an increase in exercise tolerance and sense of well-being.

Hemodynamic studies revealed a decrease in heart rate, cardiac index, oxygen consumption, brachial and pulmonary artery pressures, minute external ventricular work, and minute ventilation. There was an increase in stroke index, arteriovenous oxygen difference, and systemic resistance.

The hemodynamic changes clearly substantiate and provide an explanation for the symptomatic improvement noted by the patients. These results support the usefulness of iatrogenic hypothyroidism in the treatment of severe heart failure.

Interrelation Between Coronary Hemodynamics and the Electrocardiogram During Exercise

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By means of coronary sinus catheterization, nitrous oxide coronary flow, and coronary venous oxygen measurements, the relationship between coronary insufficiency and electrocardiogram changes in the resting and exercise states has been investigated in man. Physiologic studies were carried out during the resting state in 88 patients, while 43 were studied during both rest and exercise. All patients had resting electrocardiograms, and all those who underwent exercise coronary flow studies had standard Master tests as well.

Fourteen patients had a negative Master test, of whom 11 had normal coronary flow studies. Twenty-six patients had a positive Master test, of whom 10 had normal flow studies, 14 abnormal, and 2 equivocal. Three patients had equivocal Master tests. If those patients on digitalis are eliminated, then all 9 patients with negative Master tests had normal flow studies, and of the 8 patients with a positive Master test, 6 had abnormal coronary flow studies and 2 normal. Thus, in the undigitalized patient there is a good correlation between the interpretation of physiologic and electrocardiographic tests of coronary vascular status.

Those patients studied only at rest were grouped according to whether or not they had chronic S-T segment depression and were further divided into those on or off digitalis. There was little variation between groups, with an over-all average coronary venous saturation of 28.1 per cent, and no statistical difference between them. Thus, myocardial ischemia, as indicated by electrocardiographic abnormalities at rest, cannot be specifically correlated with decreased coronary venous oxygen saturation. The correlation between the exercise electrocardiogram and exercise coronary flow studies appears to be good, although the number of patients studied is quite small.

Diagnosis of Pericardial Effusion by Radioisotope Scanning

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In 1950 an instrument was developed that could measure the spatial distribution of radioactive iodine in the thyroid gland. Since that time several different radioisotope-scanning devices have been developed and applied to problems in medical diagnosis. It is now possible to construct scanning devices capable of detecting small differences in spatial distribution of radioactivity in internal organs and presenting the data in a form that can be readily interpreted.

Using an automatic photoscanning technic, we have studied a series of 35 patients in whom the differentiation of cardiac dilatation and/or hypertrophy from pericardial effusion was not certain by clinical means. The spatial distribution of human serum albumin labeled with radioactive iodine was measured. The resulting photoscan was superimposed over a chest roentgenogram made simultaneously. Four criteria permitted diagnosis of pericardial effusion: (1) 8 of 11 patients with pericardial effusion had a zone of decreased radioactivity separating the increased vascularity of the heart from the lung fields; (2) 10 patients with pericardial effusion had a marked separation of hepatic and cardiac silhouettes, while in contrast cardiac and hepatic distributions of radioactivity fused without separation in normal persons and patients with cardiomegaly; (3) in patients with cardiac dilatation the cardiac silhouette on photoscan was greatly enlarged; (4) in 11 patients with pericardial effusion, the ratio of cardiac diameter measured by cardiac photoscan to cardiac diameter measured by routine roentgenograms was 57 ± 12 per cent (1 S.D.). In patients with cardiac dilatation the ratio was 91 ± 7 per cent (1 S.D.).

Relative Lack of Potentiation of Norepinephrine by Arfonad

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When ganglia are blocked, norepinephrine elevates blood pressure more than usual and increases the pulse. These effects are considered to be due to abolition of previous buffering autonomic activity by ganglionic paralysis. If the norepinephrine hypertension were not pronounced, would it prompt autonomic buffering, and would blood levels of norepinephrine be influenced by variations in autonomic function?

Ten subjects were given constant infusions of norepinephrine, 4 μg./min., for 65 minutes. Intra-arterial blood pressure and pulse were continuously recorded. After 20 minutes, infusion of the ganglionic blocker, Arfonad, was begun and clinical ganglionic paralysis produced for 45 minutes. Then norepinephrine was stopped, but Arfonad was continued at a constant rate for 20 minutes more. Two sets of arterial and femoral venous blood samples were collected during a control period, during norepinephrine alone, during norepinephrine plus Arfonad, and during Arfonad alone. These were analyzed for norepinephrine by a previously reported, sensitive fluorometric method.

Norepinephrine caused small increases in blood pressure and decreases in pulse in all subjects. The addition of Arfonad further increased the mean blood pressure only 5/5 mm. Hg but increased the average pulse 22 beats/min. Arterial levels of infused norepinephrine were unchanged by Arfonad, but femoral venous levels were slightly but significantly raised, probably because of a greater flow through skin.

Autonomic cardioinhibitory activity but not depressor activity is significant during norepinephrine infusions when the blood pressure and pulse are nearly physiologic. Autonomic activity is not concerned with the breakdown of infused norepinephrine; if sympathetic paralysis potentiates norepinephrine at these levels, it does so by removing buffering activity, not by increasing blood levels.

Substitution of Normal Sympathetic Pressor Function by Norepinephrine

John M. Wallace, Durham, N. C., and Arnold M. Weissler, Galveston, Texas

Sympathetic activity is necessary to maintain normal blood pressure which falls when ganglionic paralysis occurs. Norepinephrine can effectively replace this function. If exactly enough norepinephrine were infused to restore blood pressure to normal during sympathetic paralysis in normal resting subjects, one could obtain an estimate of the circulating level of norepinephrine necessary to substitute for this sympathetic pressor function, which does not depend on circulating norepinephrine.

In 10 men blood pressure was continuously recorded, and multiple samples for norepinephrine determinations were collected. Norepinephrine, 4 μg./min., was given intravenously. The average increase in blood pressure was 17/12 mm. Hg. Ganglionic blockade was produced with trimethaphan camphorsulfonate while norepinephrine was continued. Average blood pressure was further elevated 5/5 mm. Hg. Norepinephrine was stopped and the blocking agent continued, the average blood pressure fall being 35/16 mm. Hg below normal. The average arterial plasma concentration of infused norepinephrine was 0.0064 μg./5 cc. and

was unchanged during ganglionic paralysis.

The data showed the following:

1. Ganglionic blockade slightly increased the blood pressure rise from small norepinephrine infusions.

2. The added blood pressure elevation could be due to absence of sympathetic depressor buffering or increased sensitivity of receptors to norepinephrine but could not be due to slower destruction of the substance, the arterial concentration of which was unchanged.

3. During blockade, infusions which increased the blood pressure 35/16 mm. Hg would have replaced the absent sympathetic pressor activity. Our infusions exceeded that blood pressure by 17/12 plus 5/5 mm. Hg; less than 4 μg./min. would have sufficed.

4. The arterial plasma level of norepinephrine which would have compensated for absent sympathetic pressor activity would have been less than 0.0064 μg./5 cc.

Evaluation of Mitral Commissurotomy for the Prevention of Systemic Embolism in Mitral Stenosis

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Commissurotomy has been advocated as prophylaxis against systemic embolization in patients with predominant mitral stenosis who have had previous emboli. To evaluate this procedure, 100 consecutive patients with mitral stenosis and documented preoperative arterial embolizations who had undergone commissurotomy were analyzed. The follow-up period averaged 29.5 months. Atrial fibrillation was present in 93 patients, sinus rhythm in 7.

Forty of the 100 patients had intraoperative and postoperative systemic embolizations; of these, 20 were postoperative. Commonest sites were the carotid system and aortic bifurcation. In 12 patients whose primary indication for surgery was previous embolism, there was one postoperative embolus. In 38 patients where this was one of the indications, 26 per cent subsequently embolized. In 50 patients where pulmonary congestion was the chief indication, 13 per cent embolized. Preoperative anticoagulation reduced the incidence of embolization from 60 per cent in patients without anticoagulation therapy to 16 per cent in the 45 patients with anticoagulants. Valve area, amputation of the atrial appendage, and intraoperative occlusion of the carotids did not significantly affect the outcome, whereas a good valve split, absence of atrial clots, and appreciable lapse between the last preoperative embolus and time of surgery were favorable factors.

It would seem that in patients with mitral stenosis who have had previous emboli, the threat of further emboli is considerable even after commissurotomy, but where this is not associated with congestive failure, the outlook is better. Atrial fibrillation itself may well predispose these patients to further embolization.

Diagnosis of Congenital Heart Disease from Clinical Data with a Digital Computer

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The estimated probability of each of 63 "symptoms" (age group, complaints, physical signs, electrocardiogram, and x-ray findings) occurring in each of 33 congenital heart diseases was punched on cards. A Burroughs 205 digital computer was programmed to calculate from this information the likelihood of each disease in the presence of any given combination of symptoms. A basic equation from probability theory called Bayes theorem was used for this calculation. (The possibility of applying this equation to medical diagnosis was first suggested by Ledley and Lusted.)

Experience with this approach to date has shown:

1. The computer does make a diagnosis from clinical data which agrees well with the diagnosis made by a group of experienced clinicians.

2. If the printed list of diagnoses provided by the computer contains no one diagnosis whose probability approaches 1.0, additional information is required for the computer (or the physician) to come to a more definite diagnosis. On the other hand, if one disease in the list has a probability approaching 1.0, no further studies are required.

3. The contribution made by any one symptom toward establishing a diagnosis may be quantitatively evaluated by comparison of the differential diagnosis made by the computer with and without this symptom.

4. Modification of the punched-card data to include other symptoms or new information from current medical literature is readily accomplished.

5. From its own experience and data supplied from physiologic studies, surgery, or autopsy, the computer can revise its earlier data regarding the incidence of symptoms in diseases and improve its subsequent performance.

Physiologic Observations During Induced Dyspnea

Albert J. Wasserman and John L. Patterson, Jr., Richmond, Va.

Any precise analysis of the genesis of dyspnea requires correlation of multiple variables with the appearance and disappearance of this symptom. Seventeen normal adult males were exercised at 500 Kg./M./min. with added airway resistance

(area 42 mm.^{2}). At the onset of dyspnea, indicated by hand signals (and described later), exercise was terminated. In 11 experiments with the subjects supine and breathing air, mean control arterial pO_2 was 95 mm. Hg and pCO_2 42 mm. Hg (bubble equilibration). Dyspnea appeared after an average of 101 seconds of exercise, at which time the pO_2 was 79 mm. Hg and pCO_2 52 mm. Hg and the average minute ventilation was 34 per cent of the maximum breathing capacity, determined with added airway resistance. At the disappearance of dyspnea 98 seconds later, the pO_2 had returned to control levels, but the pCO_2 was unchanged. Between the onset and disappearance of dyspnea the elevated minute ventilation actually increased still further in 6 subjects. In 9 experiments with the subjects breathing air, the arterial pO_2 did not fall, and dyspnea was not produced despite longer exercise, comparable rises in pCO_2, and greater increases in minute ventilation. In 6 of 8 additional experiments 100 per cent O_2 given immediately after the onset of dyspnea produced definite symptomatic relief despite continuance of exercise.

These findings support the view that dyspnea is related to the summated load of respiratory stimuli. In these experiments moderate change in arterial pO_2 apparently was a decisive factor in the appearance and disappearance of the symptom.

Postsystolic Myocardial Augmentation: Experimental Development and Clinical Results in Six Cases

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A method has been devised by means of which the work load of the myocardium may be electively decreased in pathologic conditions while at the same time the coronary arterial flow is increased without reduction of the total circulating blood volume. A special mechanical apparatus provides an atraumatic impulse to each unit stroke volume of the cardiac output in conjunction with a device which synchronizes the output of the assisting mechanism with the desired phase of the cardiac cycle according to the specific need of the hemodynamic situation. The volume, length, and phase of the augmenting impulse may be varied to adapt to the hemodynamic situation.

Experimental methods included electrocardiographic and manometric studies of failing hearts before, during, and after the application of the apparatus for postsystolic myocardial augmentation. This apparatus has been used for various clinical conditions, and 6 patients with myocardial insufficiency of different types were treated by the technic. The beneficial results obtained were demonstrated by electrocardiographic and manometric studies.

Studies on the Effects of a Vasopressor Agent, Sympatholytic Drugs, and Corticosteroid in Shock Caused by Bacterial Toxin

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A vasopressor agent (metaraminol), sympatholytic drugs (phentolamine, dibenzyline), and corticosteroid (prednisolone phosphate) were used in the treatment of shock produced by injection of an approximately lethal amount of *E. coli* cells into adult dogs. The therapeutic agent was administered 15 minutes after shock had occurred.

Single intravenous injections of phentolamine (10 mg./Kg.), dibenzyline (2.5 mg./Kg.), and prednisolone (20 mg./Kg.) were employed. Metaraminol was administered by intravenous infusion (50 mg./L.) to maintain mean arterial pressure at a level 20 mm. less than control value for a period of 2 hours. In each experiment one animal was treated, and the other served as a control. A total of 82 dogs was studied. Arterial pressure, venous pressure, heart rate, urine flow, hematocrit, pH, serum transaminase, survival, and pathologic changes in the nonsurvivors were observed.

The vasopressor agent and corticosteroid increased the period of survival and the number of survivors. Sympatholytic drugs decreased survival. Combined use of the vasopressor agent and corticosteroid provided the best survival data ($p = .01$) and minimized injury as reflected in less elevation of serum transaminase, less blood pH reduction, and maintenance of almost normal output of urine. Pretreatment with corticosteroids or with adrenergic-blocking drugs has been shown by others to protect against the lethal effects of endotoxin. In the present experiments corticosteroid was effective for treatment of endotoxic shock. However, these studies do not support the conclusion that sympatholytic drugs are beneficial *after* the onset of shock or that the judicious use of a sympathomimetic drug as a vasopressor agent promotes irreversibility of the shock state.

Reduction of Cardiac Work During Venoarterial Perfusion

Max H. Weil, Milford G. Wyman, and David H. Blankenhorn, Los Angeles, Calif.

In the fetus the head and upper extremities receive blood of higher oxygen content than the lower half of the body which receives flow largely from the ductus arteriosus. The fetal system of circulation was simulated to study the effect of venoarterial perfusion in anesthetized adult dogs. Blood was passively drained from the inferior vena cava by way of both femoral veins. This blood was continuously infused through a catheter inserted from the femoral artery into the a-

dominal aorta at its bifurcation. The system was adjusted so that approximately 40 per cent (40 cc./Kg./min.) of the initial cardiac output (98 cc./Kg./min.) was provided by the extracorporeal system.

Indicator dilution and oxygen saturation measurements showed that the output of the heart was reduced by an amount which was approximately equal to the output of the pump. In the aorta an abrupt change in oxygen saturation occurred 5 cm. cephalad to the infusion catheter. A prominent continuous murmur was detected at this site. The pulse rate, peripheral resistance, and central blood volume were reduced. Cardiac output was decreased to 55 per cent and stroke work to 41 per cent of the control value. There was a slight fall of pH and pCO_2 of arterial blood. Perfusion periods in excess of 3 hours were compatible with survival. These studies confirm that the fetal system of circulation is tolerated by the adult animal and that partial perfusion with venous blood provides a technic for temporary reduction of the cardiac work load.

Cardiodynamic Effects of Experimental Bundle-Branch Block in the Dog

James R. Wennemark, David F. Blake, and Paul Kezdi, Chicago, Ill.

There is disagreement as to whether experimental bundle-branch block produces a delay in contraction of the blocked ventricle.

The present study was undertaken to evaluate this problem by means of direct ventricular pressure measurements in the closed chest dog with acute and chronic experimental bundle-branch block.

Two series of experiments were performed:

1. Simultaneous right and left ventricular pressure curves were recorded by percutaneous transthoracic catheterization. Bundle-branch block was then produced by interrupting the bundle branch, which was visualized with an open heart procedure. The catheterization study was repeated after a 3 to 4-week interval.

2. A suture was placed around the bundle branch with an open heart procedure and fixed to the outside of the chest. After a 3 to 5-day interval simultaneous right and left ventricular pressure curves were recorded with the above technic, while transient bundle-branch block was produced by tension on the suture.

Results were similar in both types of experiment. Eighteen successful preparations involving right bundle-branch block and 20 involving left bundle-branch block were obtained. The beginning upstrokes of the ventricular pressure curves were used to determine the onset of right and left ventricular contraction, and a delay was consistently found in the blocked ventricle as compared with the control. This averaged .02 second with either right or left bundle-branch block. The second type of experiment allowed numerous reproducible observations in a preparation without catheter manipulation. In this type of experiment a change in the contour of the right ventricular pressure curve was usually discernible in right bundle-branch block.

Right and left bundle-branch block produces a delay in contraction of the ventricle on the blocked side.

Mast Cell Alterations in the Myocardium of Atherosclerotic Rats

Bernard C. Wexler, Thomas E. Brown, and Benjamin F. Miller, Cincinnati, Ohio

It has been suggested that connective tissue mast cells may be related to the development of atherosclerosis because patients with this disease show a smaller number of mast cells than normals. In addition, the atherosclerosis-resistant rat possesses a high number of mast cells in the myocardium while the more susceptible rabbit and chicken contain a low number. Repeated breeding without rest between litters will produce atherosclerosis in the rat. The authors have found that unilateral nephrectomy and injection of ACTH intensify and increase the incidence of arteriosclerosis. Animals selectively bred and sacrificed after successive breedings demonstrate progressive accumulation of acid mucopolysaccharides and subintimal fibrosis. Continued breeding and injection of ACTH coupled with uninephrectomy cause greater pooling of mucopolysaccharides and fibrosis along with accelerated arteriosclerosis. Myocardial tissue from male and female breeder rats was stained with toluidine blue and studied in conjunction with the progressive development of the atherosclerosis. As the atherosclerosis became more pronounced, the population of myocardial mast cells decreased. ACTH and uninephrectomy aggravated the atherosclerosis and caused the greatest decrease in myocardial mast cells; the reaction of mast cell granules was changed from metachromatic to orthochromatic, indicating the likelihood of active secretion without cellular lysis. It appears that mast cell granule discharge is influenced by secretory activity of the adrenal glands. Also it seems possible that the discharge and disappearance of myocardial mast cells may contribute to the accumulation of mucopolysaccharides in the experimental arterial lesions.

Usefulness of the Vectorcardiogram in the Diagnosis of Atypical Myocardial Infarction

Conger Williams and Donald McCaughan, Boston, Mass.

One thousand vectorcardiograms have been taken at the Cardiac Laboratory, Massachusetts General Hospital, each with at least 2 of the recognized lead systems. Cube and tetrahedral systems were used until 1959. Since then vectorcardiograms using the cube and Frank systems along with the standard electrocardiogram have been taken on each patient. More than 200 have been taken on patients with myocardial infarction, old or recent, proved by characteristic clinical course or by autopsy.

As a result of this experience, we conclude that the technic is very useful in diagnosis of atypical myocardial infarction. This paper summarizes 20 of these cases.

For many years the finding of Q waves in the standard electrocardiogram was considered essential to diagnosis of myocardial infarction. More recently it has become known that destruction of cardiac muscle in certain parts of the heart ("true posterior" and lateral infarcts) may produce patterns in the standard electrocardiogram which represent infarction without characteristic Q waves. In such instances the vectorcardiogram is often useful in establishing a diagnosis of infarction and in helping the electrocardiographer to understand atypical patterns.

Vectorcardiography has also helped in the understanding of complicated patterns combining bundle-branch block with infarction.

The characteristic alterations of vector loops produced by infarcts in an unusual location were well demonstrated in this series of cases.

Digitalis in Experimental, Surgically Induced Heart Block

Vallee L. Willman, Hector S. Howard, and C. Rollins Hanlon, St. Louis, Mo.

The effect of digitalis on circulatory dynamics has been studied in 15 dogs with complete heart block produced by ligation of the bundle of His.

Measurements have been made of left atrial pressure, cardiac output, cardiac rate, coronary flow, systemic pressure, right atrial pressure, pulmonary artery pressure, myocardial oxygen utilization, and isometric ventricular tension.

Digitalis in the usual dosage of 0.03 mg./Kg. reduced cardiac rate and lowered cardiac output slightly. Stroke work remained the same or was increased. Isometric ventricular tension and myocardial oxygen consumption were unchanged. Atropine abolished the slowing, suggesting that there is a vagal effect acting distal to the A-V node.

Digitalis given in amounts greater than 0.05 mg./Kg. resulted in tachycardia. The increase in rate varied from 10 beats per minute up to a tachycardia of 180 per minute. This increased rate was associated with increased cardiac output up to 4 times the predigitalization level. Isometric ventricular tension was increased up to 2 times control values.

In 10 of the animals with complete heart block, the rate was accelerated by external electrical stimulation. Use of digitalis in these 10 animals did not decrease the cardiac output in any instance; in 5 of them the cardiac output was increased by digitalis.

These experiments suggest that the use of digitalis should be considered in instances of complete heart block induced by surgical procedures.

Effect of Temperature on Ventricular Function in the Dog with Complete Heart Block

Vallee L. Willman, Hector S. Howard, and C. Rollins Hanlon, St. Louis, Mo.

The evaluation of ventricular function curves at varying temperature levels is complicated by the bradycardia of hypothermia and the tachycardia of hyperthermia. To obviate the rate changes incident to temperature shifts, we produced complete heart block in 5 dogs by ligation of the bundle of His and maintained a constant heart rate by an electronic stimulator. The body temperature was varied from 30 to 41 C. by means of a blood heat exchanger introduced between a femoral artery and a femoral vein.

In these animals we have recorded dye dilution cardiac outputs, systemic pressure, left atrial pressure, right atrial pressure, pulmonary artery pressure, and isometric ventricular tension.

Ventricular function over the temperature range of 30 to 38 C. did not vary greatly. Cardiac output fell as the temperature was lowered, but stroke work at a given left atrial pressure remained essentially the same. Isometric ventricular tension also remained constant. As the temperature was increased above 40 C., there was a distinct fall in stroke work, cardiac output, and isometric ventricular contraction.

This study emphasizes the importance of avoiding hyperpyrexia in patients with fixed cardiac rates who cannot respond to demands for increased cardiac output by increasing their cardiac rate.

Evidence for Two Mechanisms of Hypotensive Action of Diuretics

Bertram M. Winer and Bal M. Sahay, Boston, Mass.

Studies were undertaken to determine the separate roles of deficits of sodium, potassium, and plasma volume in the hypotensive action of benzothiadiazines.

Plasma volume deficits were restored by dextran in 20 hypertensive subjects receiving thiazides.

Systolic blood pressure rose toward but did not reach control levels; diastolic values remained at the lower levels induced by the diuretic.

Responses to norepinephrine, trimethapan, and erythrol tetranitrate were determined in 10 hypertensive subjects during placebo administration, after 2 weeks of hydrochlorothiazide daily, after dextran, and 1 week after 20 Gm. of added salt daily. The pressor response to norepinephrine was reduced, and depressor responses to trimethaphan and erythrol were increased by hydrochlorothiazide. Replenishment of plasma volume lessened the effects of the diuretic on systolic responses to the vasoactive substances but had little effect on diastolic responses. With replenishment of sodium basal blood pressure, body weight, and responses to vasoactive substances reverted to control levels, but exchangeable potassium remained low.

The hypotensive action of diuretics results fundamentally from sodium deficit irrespective of plasma volume deficit. Reduction in plasma volume plays an important auxiliary role, influencing the fall in systolic pressure and strongly affecting the responses of other drugs that alter effective blood volume. Potassium deficit was not significant in the hypotensive action.

Relative increments in blood pressure evoked by norepinephrine were greater in the diuretic and dextran periods of study than in the placebo or salt periods, suggesting that salt depletion may not reduce arteriolar responsiveness to pressor substances directly but may act by a humoral or neurogenic mechanism.

Hypotensive Effects of Nitrites During Diuretic Therapy

Bertram M. Winer and Bal M. Sahay, Boston, Mass.

The hypotensive effects of nitroglycerin and erythrol tetranitrate were examined in 16 hypertensive patients before and during daily administration of hydrochlorothiazide. Blood pressure (standing) fell from 196/118 to 166/106 mm. Hg after nitroglycerin alone; the erythrol response was similar in degree. During hydrochlorothiazide administration both nitrites had striking hypotensive effects, which were maximal in the standing position. After nitroglycerin blood pressure fell from 177/106 to 132/88 ($p < .01$), after erythrol from 166/105 to 129/82 ($p < .01$). In 3 patients both nitrites induced blood pressure falls to less than 90/65, and syncope occurred. The onset of hypotensive action after nitroglycerin occurred within 2 minutes; duration was less than 45 minutes. The action of erythrol occurred within 20 minutes; duration varied from 2 to 5 hours.

Plasma volume replenishment by dextran diminished the fall of systolic pressure but did not affect diastolic response to nitrites during diuretic administration. Salt replenishment prevented and elastic stockings reduced the hypotensive response.

These studies: (1) provide an objective method for comparative bioassays of different nitrites in man; (2) establish that nitroglycerin and erythrol tetranitrate have different durations of action; (3) suggest that addition of nitrites to diuretics may be useful in the treatment of hypertension; (4) show that excessive hypotension due to nitrites can be prevented by elastic stockings; and (5) demonstrate that diuretics influence the hypotensive response to nitrites by 2 mechanisms, one related to reduced volume flow and the other to sodium loss independent of the reduced plasma volume.

Syncope will be encountered not infrequently in ambulatory patients given nitrites during continuous diuretic therapy.

Effects of Feeding Fats with Varying Fatty Acid Composition on the Blood and Tissue Lipids of Cebus Monkeys

Robert W. Wissler, Randolph H. Hughes, Laurence E. Frazier, and Richard A. Rasmussen, Chicago, Ill.

Two previous experiments have demonstrated the effects of hydrogenation of food fats on the blood and tissue lipids of the Cebus monkey. The current experiment included 3 groups of 4 monkeys fed equal quantities of 3 diets which varied only in the lipid components. Butterfat, coconut oil, and corn oil were the 3 fats used, each making up 25 per cent of the ration. The experiment lasted for 45 weeks, and the animals were bled, their gallbladders drained, and their livers and adipose tissues biopsied at 15-week intervals. At each of these intervals, they received C^{14} acetate i.v., and they were fed equal daily doses of H^3 cholesterol throughout the experiment. The animals receiving the butterfat and the coconut oil rations showed a prompt and sustained rise in serum cholesterol (varying from 341 mg. per cent to 418 mg. per cent) while those receiving the corn oil demonstrated less change from the baseline values (256 mg. per cent as compared to 161 mg. per cent). Other serum lipids showed similar trends. Bile acid patterns and the patterns of fatty acids esterified with cholesterol, as well as other blood and tissue lipid fractions, were correlated with the specific activity and synthesis rates of cholesterol in various organs and tissues. Pertinent pathologic findings were also correlated with the blood and tissue lipid values and with the tracer data.

Genetic, Clinical, and Physiologic Observations in Milroy's Disease

J. Edwin Wood, Augusta, Ga., John R. Esterly, and Victor A. McKusick, Baltimore, Md.

The genetic transmission of Milroy's disease (chronic hereditary lymphedema) was studied in 4 families. The pedigree patterns were compatible with an autosomal dominant trait with complete penetrance but variable expressivity. Studies of blood groups, serum haptoglobins, PTC tasting, and isoniazid metabolism in one family demonstrated no evidence of linkage.

Edema was present at birth in 16 patients and appeared around puberty in 4. Involvement of one or both lower extremities, of the feet, or of only 2 fingers was observed. Extent of edema varied from an almost unnoticeable pretibial swelling to that which hampered ambulation by its weight. Affected limbs were warm, and there were no trophic changes of the skin. Biopsy revealed numerous clusters of arterioles deep in the dermis.

Calf blood flows were measured plethysmographically in Milroy's disease, normal subjects, and patients with edema from other causes. Mean blood flow (MBF) in ml./min./100 ml. of calf tissue including the edema was 8.1, σ 7.8, range 2.8 to 31.4 in 14 patients with Milroy's disease. MBF of 11 normal subjects was 2.2, σ 1.2. MBF of 3 patients with acquired lymphedema was 1.8, range 1.1 to 2.2. MBF of 14 patients with equally extensive edema from other causes was 2.2, σ 1.3. Dissipation of edema in 3 patients with Milroy's disease resulted in change of MBF from 15.0 to 8.1, 14.9 to 4.7, and 5.1 to 8.4. These studies suggest that Milroy's disease is characterized by a chronic hyperemia that not only contributes to formation of edema but is secondarily accentuated by the edema.

Bacterial Endocarditis in Infants and Children

Charles F. Wooley and Don M. Hosier, Columbus, Ohio

Clinical and laboratory findings in 21 infants and children with bacterial endocarditis were reviewed. Seventeen had congenital heart disease, 4 had no organic heart disease, and none had rheumatic heart disease.

Initiating factors included surgical procedures, dental extractions, and preceding infectious processes. Fever (100 per cent), murmur (76 per cent), positive cultures (71 per cent), severe anemia (67 per cent), and the suggestive clinical history were emphasized. Significant emboli constituted a poor prognostic sign.

The congenital malformations encountered were as follows: ventricular septal defects (5), tetralogy of Fallot (5), patent ductus arteriosus (3), coarctation of aorta (1), coarctation and patent ductus (1), subaortic stenosis (1), and pulmonic stenosis (1). Exact localization of the endocarditis or endarteritis was proved 9 times: tricuspid valve (5) ventricular septal defect (1), coarctation (1), subaortic stenosis (1), and aortic valve (1). Four patients (3 infants) without pre-existing heart disease had tricuspid bacterial endocarditis.

Etiologic organisms were obtained in 17 patients. The staphylococcus (38 per cent) and the miscellaneous organisms (24 per cent) outnumbered the streptococcus 3 to 1.

Of 170 children undergoing open heart surgery for congenital heart disease, 4 developed bacterial endocarditis postoperatively. Two children manifested fulminating processes 3 days postoperatively (*Staphylococcus aureus*, beta streptococcus), while the others presented with a less fulminant picture one month postoperatively (*Staph. aureus*, micrococcus).

Of 13 surviving patients (62 per cent), 12 were over 2 years of age. Nine have been followed for an average of 5 years; none has shown evidence of significant myocardial degeneration.

Supravalvular Aortic Stenosis: Experences with Three Young Males

Charles F. Wooley, Don M. Hosier, Richard W. Booth, William Molnar, Howard D. Sirak, and Joseph M. Ryan, Columbus, Ohio

Supravalvular aortic stenosis represents a heterogeneous grouping of 2 or possibly 3 congenital entities producing left ventricular outflow obstruction.

Three males (ages 13, 16, and 19) presented clinical evidence of aortic stenosis; one also had aortic insufficiency. Systolic pressure differences in the arms of all 3 showed an inconsistent pattern. Fluoroscopy showed left ventricular hypertrophy without poststenotic dilatation of the ascending aorta. Electrocardiograms indicated left ventricular hypertrophy.

The first case was diagnosed at surgery; attempt at correction was unsuccessful. Necropsy showed a hypoplastic annulus, a discrete narrowed area just above the valve, and moderate hypoplasia of the ascending aorta.

Two patients had left ventricular catheterization, levocardiograms, and supravalvular aortography. Ventriculoaortic systolic gradients of 170 and 12 mm. Hg were found. Roentgenographically one had a narrowed, short segment of the ascending aorta 2.5 cm. distal to the cusps and normal coronary arteries proximal to this segment. The second showed a ringlike narrowing across the level of the

coronary ostia. There was mild aortic regurgitation and a poorly visualized right coronary artery. Previous experience with this entity and unsuccessful attempts at surgical repair make it mandatory to perform aortography in patients with congenital left ventricular outflow obstruction without poststenotic aortic dilatation, especially in males with systolic pressure differences in the arms. Three cases of supravalvular stenosis in 9 months suggests a higher frequency than is generally expected with this entity. Aortic stenosis in a sibling of one patient suggests a possible familial tendency. The diagnosis is roentgenographic.

Evaluation of Rapid Diagnosis of Group A Streptococci by Fluorescent Antibody Technics

Donald A. Yarashus and Alan C. Siegel, Chicago, Ill.

This study compared the conventional precipitin method of grouping β-hemolytic streptococci with the fluorescent antibody technic of identification of group A streptococci from the sediment of a 2-hour broth culture previously inoculated with a direct throat swab.

Specific points of comparison included the accuracy of this method and the practicality of application to a routine bacteriology laboratory. Previous pilot studies indicated that the immediate fluorescent staining of a smear from a direct throat swab failed to correlate well with the conventional grouping method.

Three hundred and seventy-six cultures were obtained from children with acute or convalescent pharyngitis, who were part of a controlled study now in progress at the Children's Memorial Hospital. One hundred and thirty-two of 376 cultures were positive for group A streptococci by the precipitin method. In all but 14 (10 per cent) of these cultures, the fluorescent antibody gave positive confirmatory results for group A streptococcus. Fifteen strains of β-hemolytic streptococci were nongroup A by the conventional method. Positive fluorescent antibody tests were obtained on 5 of these. There were 229 cultures negative for β-hemolytic streptococci. Twenty-three (10 per cent) revealed positive fluorescent antibody reactions.

Specific problems in technic encountered with this method include: (1) a time interval of 4 hours, necessary in order to process broth cultures for fluorescent surveys, which meant that cultures had to be in the laboratory by 1 p.m. in order to obtain results on the same day; and (2) fatigue of the individual surveying the fluorescent fields, thus limiting the number of determinations possible in a single day.

It is concluded that there were 10 per cent false positive and 10 per cent false negative fluorescent antibody reactions encountered. Whether these represent nonviable organisms or nonhemolytic group A streptococci is yet undetermined.

Responses in Abdominal Muscles Elicited by Sudden Changes in Central Blood Volume

William B. Youmans, Larry D. Davis, Dorothy I. Briggs, and Kenneth L. Goetz, Madison, Wis.

Effects of vasodilator agents (nitroglycerin and urecholine), vasoconstrictor agents (vasopressin and phenylephrine), rapid bleeding, and obstruction of the inferior vena cava, the pulmonary artery, or the ascending aorta on activity of abdominal muscles and the level of intra-abdominal pressure have been studied in dogs under sodium pentobarbital anesthesia. Steady-state contractions of abdominal muscles, which are present from the time of completion of the characteristically rapid expiration until just before the onset of the next inspiration, and intra-abdominal pressure show a sudden marked increase when venous return is blocked by inflation of a balloon on a catheter tip in the thoracic portion of the inferior vena cava. Blockage of the ascending aorta by the same device causes, after a brief latent period, a decrease in activity of abdominal muscles. Blockage of the pulmonary artery by the same method has an effect similar to that produced by blockage of the inferior vena cava. Bleeding or injection of vasodilator agents elicits a sudden increase in steady-state contractions of abdominal muscles, and injection of vasoconstrictor agents has the opposite effect. The procedures which cause a decrease in volume of blood in the heart and lungs elicit an increase in steady-state activity of abdominal muscles and a corresponding rise in intra-abdominal pressure. Other procedures which cause a rise in central blood volume inhibit abdominal muscles. This constitutes a mechanism by which any sudden deficiency or excess of venous return can be counteracted instantaneously.

Hemodynamic Effects of Angiotensin in Man

Paul N. Yu, Milton N. Luria, James K. Finlayson, and C. Alpheus Stanfield,† Rochester, N. Y.

Hemodynamic effects of angiotensin given by intravenous infusion at a rate of 0.028 to 0.135 μg./Kg./min. were studied in 16 normotensive patients without mitral valvular lesions. During angiotensin infusion the following changes were observed: (1) prompt increase in systemic artery, pulmonary wedge ("PC_m" or LV_D), pulmonary artery (PA_m), and right ventricular diastolic (RV_D) pressures, but variable change in PA_m-"PC_m" gradient; (2) decreased or unchanged car-

diac output (both by Fick procedure and indicator-dilution curves), usually manifested by a significantly widened arteriovenous oxygen difference and slightly increased oxygen consumption; (3) decreased heart rate and inconsistent change in stroke volume; (4) significant increase in total systemic, total pulmonary, and "left heart" resistance; (5) increased stroke work of both ventricles against pressure (LV_{SW} and RV_{SW}); and (6) prolonged mean transit time with increased or unaltered "central" blood volume. The increment in LV_{SW} correlated well with that in LV_D, as did RV_{SW} with RV_D.

Angiotensin causes systemic arteriolar constriction resulting in a significant increase in total systemic and "left heart" resistance. There is no evidence for compromise in the ventricular functions despite a significant rise in these 2 parameters. The increment in the pulmonary artery and right ventricular systolic pressure is largely due to an elevated left ventricular diastolic pressure. Likewise, the increment in the total pulmonary resistance is mostly secondary to an elevated "left heart" resistance. Since there is an invariable increase in the total systemic resistance but no uniform decrease in the cardiac output, it is possible that angiotensin does have inotropic action in some cases.

Hemodynamic Studies in Fourteen Cases of Tetralogy of Fallot After Complete Corrective Open Cardiac Surgery

Henry A. Zimmerman and Earle B. Kay, Cleveland, Ohio

Fourteen cases of tetralogy of Fallot have been studied before and after complete correction by the open heart technic. All 14 cases, studied within one year after surgery, were clinically improved, and all had arterial O_2 saturations in the range of normal. However, only 7 patients showed return of pressures within the lesser circulation to the normal range.

Five patients had significant reductions in their lesser circulation pressure but still had moderate elevation of pressures and gradients across the pulmonary valve. Two patients showed no change in their hemodynamics following surgery but had normal O_2 saturations. One has since died of congestive cardiac failure and subacute bacterial endocarditis.

The reasons for poor results were: (1) inadequate outflow reconstruction due to anatomic location of the right coronary artery; and (2) inadequate development of pulmonary circulation and inability to establish right ventricular outflow. All cases for surgery should have selective cineangiocardiographic studies to define the anatomy more clearly and in detail.

SCIENTIFIC EXHIBITS

All Exhibits will be Displayed in Kiel Auditorium

Cardiac Vibration Analysis. *Clarence M. Agress, Louis G. Fields, Morris Wilburne, Martin D. Shickman, and Stanley Wegner, Los Angeles, Calif.*

This exhibit is designed to show the background and applications of precordial vibrations. The technic employed in making tracings of the heart's vibrational energy is demonstrated. These vibrations are separated into frequency bands (the spectrosonogram). Finally, possible application of this technic to the early diagnosis of heart disease is indicated.
(Booth S-26)

Cardiac Laminography. *Hernan Alvarez, Jr., and William Eyler, Detroit, Mich., Kenneth McGinnis, Lexington, Ky.*

Laminograms are used to demonstrate intracardiac calcifications and its location. With this system, valvular calcification can be separated as to the anulus and valve proper. Ease of separating calcification from mitral and aortic valves is also facilitated.
(Booth S-1)

Reference Laboratory and Central File for Rare Donors. *American Association of Blood Banks, Miami, Fla.*

Animated exhibit depicting 2 major services of the association: the reference laboratory for identification of rare blood types and the rare donor file for information relative to transfusions of uncommon types of blood.
(Booth S-7)

Clinical and Experimental Studies in the Treatment of Thrombotic Disorders. *William G. Anlyan, Donald Silver, and Hugo L. Deaton, Durham, N. C.*

The exhibit portrays our changing concepts in the treatment of thrombotic diseases. It is based on our experience of over 700 patients with thromboembolic disease and over 400 dog experiments in the prevention of rethrombosis of intimectomized arteries. With the availability of fibrinolytic agents, it has been possible to lyse fresh clots as well as keep them from propagating with the routine anticoagulant drugs. Our series includes 30 patients treated with fibrinolytic agents, including 11 with fresh arterial occlusions in whom objective evaluation could be carried out. In 10 of the 11, there was a return of distal pulses with salvage of all or part of a limb. It appears that fibrinolytic agents are a useful adjunct to accepted surgical procedures.
(Booth S-3)

Thrombus Formation in Blood Vessels of Small Laboratory Animals Studied Microscopically. *James D. Blanding, Jr., and Raymond L. Henry, Charleston, S. C.*

Studies have included the morphologic constituents involved in thrombus formation, spatial relationships of blood elements to developing thrombi, and changes with time. The in vivo observations were made up to 12 hours after trauma to vessel walls, while the freeze-substitution allowed development of thrombi up to 7 days.
(Booth S-5)

Newer Approaches to Antihypertensive Therapy. *Albert N. Brest and John H. Moyer, Philadelphia, Pa.*

The newer approaches to antihypertensive therapy include the use of drugs which: (1) affect catecholamine release, e.g., guanethidine; (2) interfere with enzymatic activity, e.g., the monoamine oxidase and decarboxylase inhibitors; or (3) alter fluid and electrolyte balance, e.g., the thiazide derivatives. The mechanisms of action and clinical use of these drugs are described.
(Booth S-31)

Treatment of Thrombo-Embolic Diseases with Fibrinolysin. *Eugene E. Cliffton and Carlo E. Grossi, New York, N. Y.*

This exhibit consists of 4 parts: Part 1 shows the source and activation of fibrinolysin. Part 2 consists of animal experimental work showing the effects of fibrinolysin on thrombi of varying duration. Pictorial demonstration and charts. The central panel depicts the microscopic changes with formation of and lysis of a thrombus. Photomicrographs, drawings and schematic. The remaining 2 parts report results in clinical cases, complications seen and schedules of treatment. Illustrative cases of venous and arterial thrombosis are shown.
(Booth S-4)

Selective Visceral Arteriography. *Robert N. Cooley, John R. Derrick, and Colvin H. Agnew, Galveston, Texas*

This exhibit demonstrates the technic and results of selective radiographic visualization of the celiac axis, superior mesenteric and renal arteries and their smaller branches. Application of this technic to the investigation of mesenteric vascular insufficiency and hypertension associated with renal artery obstruction will be emphasized. **(Booth S-6)**

Regional Circulation During Cardiac Arrhythmias. *Eliot Corday and David W. Irving, Los Angeles, Calif.*

The vasomotor response of the mesenteric, carotid, and renal arteries is demonstrated utilizing a new electromagnetic integrator-computer flowmeter technic. The regional circulation of these vital organs is markedly impaired during cardiac arrhythmias. A working model is used to show the instrument in use and results are shown by charts and moulages. **(Booth S-24)**

Surgery in Congenital and Acquired Heart Disease (Experimental and Clinical). *F. S. Cross, T. I. Crawford, and A. N. Gerein, Cleveland, Ohio*

The purpose of the exhibit is to show the present status of open-heart surgery in the repair of congenital and acquired heart lesions. In addition, projected accomplishments in the correction of certain acquired lesions are shown. In that portion of the exhibit devoted to congenital heart disease, the basic requirements of successful open-heart surgery, such as perfusion methods, intracardiac surgical technics, and pre- and postoperative care are shown. The common types of defects repaired are demonstrated. A continuous movie film shows surgical correction of the common defects. The currently used pump-oxygenator is in the exhibit "bypassing" a plastic heart. In the section on surgery of acquired heart lesions, the advantages and necessity of direct vision surgery are shown. Present technics in the repair of mitral stenosis and insufficiency, and aortic stenosis and insufficiency are illustrated. Current experimental work in the use of prosthetic valve replacements is illustrated, including movies of mitral and aortic valve function, with and without such prostheses. **(Booth S-14)**

Suturing of Small Arteries. *Harold S. Engler, William M. Headley, and William H. Moretz, Augusta, Ga.*

A demonstration of preferred technic in small artery suturing with emphasis on the problem of thrombosis. The incidence of thrombosis is pr- sented along with factors influencing thrombosi. Drawings and large color photographs are us to give right and wrong technic. Practical appl- cation is presented in summary. It is hoped th this will be a teaching mechanism for surgeo who may need to do a repair of the radial, uln brachial, superior mesenteric or some simil artery. **(Booth S-15)**

Medical Treatment of Varicose Ulcers and Veno Insufficiency. *William T. Foley, New Yor N. Y.*

The exhibit consists of 48 slides mounted on a automatic projector which flashes them on screen. The slides are in color and a runnin commentary describing case histories and techni is given. The treatment described is a metho that has been developed for eradicating defectiv veins by sclerosing without thrombosing them. **(Booth S-27)**

Electrical Device to Demonstrate the Blood Clotting Mechanism. *Elemér R. Gabrieli and William C. Sleight, Buffalo, N. Y.*

An electrical device to demonstrate the pathways of the blood clotting mechanism and those abnormalities encountered in the various blood clotting disorders, as well as defects brought about by both exogenous and endogenous anticoagulants, is shown. In addition, normal and abnormal laboratory tests are indicated. The newest standardized international nomenclature, complete with synonyms, is used throughout. **(Booth S-8)**

Mitral Valve. *Louis R. Head, James M. Head, Theodore R. Hudson, and Jerome R. Head, Chicago, Ill.*

The design and construction of an artificial mitral valve has resulted in new data concerning the anatomy and physiology of the normal valve. Formalin fixation of the valve opened and closed, dimensional analysis of leaflets, chordae tendinae and papillary muscles, and observation of high-speed motion pictures has produced a detailed description of the form and function of the mitral valve. **(Booth S-20)**

Experimental and Clinical Studies of the Lymphat System. *John M. Howard, Robert Bower, Cr isto Danese, Demetrios Tziros, and Joseph Debbas, Philadelphia, Pa.*

The exhibit is divided into experimental an clinical sections. Under "Experimental" are in- cluded illustrations of: (1) new technics of lym-

angiography; (2) regeneration of lymphatics; and (3) transplantation of segments of lymphatic system. Under "Clinical" are included illustrations of lymphangiograms of patients with the following conditions: (1) varicose veins, (2) thrombophlebitic syndrome, (3) thrombophlebitis, (4) primary lymphedema, and (5) postsurgical edema.
(Booth S-28)

Cineangiography, An Aid in Differential Diagnosis of Basal Diastolic Murmurs (Cineangiocardiography). *H. F. Inderlied, A. D. Nichol, and F. A. Oldenburg, Cleveland, Ohio*

This is a presentation of several intracardiac anomalies characterized by a basal diastolic murmur, including an unusual case of agenesis of the pulmonary valve. Clinical findings, electrocardiograms, x-rays, and pertinent catheterization data will be presented for each case. However, the procedure found most helpful was the cineangiocardiogram which will be projected continuously.
(Booth S-2)

Surgical Correction of Mitral Valvular Disease: An Analysis of the First 100 Patients Corrected by the Open Technic. *Earle B. Kay, Henry A. Zimmerman, and David Mendelsohn, Cleveland, Ohio*

The exhibit demonstrates: preoperative diagnostic tests with examples of altered findings; the reason and the proper time for surgical correction; pathologic factors contributing to the insufficiency; surgical technics employed in relation to pathology encountered; results of surgery in relation to operative risk; and analysis of postoperative improvement.
(Booth S-19)

High-Pressure Ventricular Septal Defect. *Jerome H. Kay, Robert M. Anderson, William E. Bloomer, John E. Meihaus, Oscar Magidson, and Edward F. Dunne, Los Angeles, Calif.*

Presenting: (1) the diagnosis of high-pressure ventricular septal defects, with tracings, diagrams and x-rays; (2) a method for the selection of patients for surgical repair of the defect; (3) the repair, a new technic, using the right atrial approach; and (4) illustrations of this technic. Statistical evaluation of the results in 100 cases of low, moderate and high-pressure ventricular septal defects.
(Booth S-18)

Conduction System in Cardiac Surgery. *Maurice Lev, William L. Riker, Arthur De Boer, Thomas G. Baffes, and Willis J. Potts, Chicago, Ill.*

The course of the A-V node, bundle, and bundle branches is described in persistent ostium primum, common A-V orifice, ventricular septal defect, and tetralogy of Fallot. Surgical methods of closure of various defects to avoid the conduction system are described, with the results obtained by these methods.
(Booth S-12)

New Control of Anticoagulant Therapy. *George A. Mayer, Kingston, Ontario, Canada*

The author's new method, the Standard Clotting Time, has proven to be an excellent guide in directing the anticoagulant therapy of 2,500 patients. No thromboembolism or bleeding occurred when the test was within the therapeutic range.
(Booth S-10)

Surgical Treatment of Renovascular Hypertension. *George C. Morris, Jr., Michael E. De Bakey, Denton A. Cooley, and E. Stanley Crawford, Houston, Texas*

Enormous strides have been made in the understanding of the physiologic and pathologic concepts of renovascular hypertension resulting from renal artery stenosis. Accelerated interest in this form of hypertension has been made possible by the development of surgical technics for direct revascularization of the kidney. This exhibit will demonstrate technics in the diagnosis of renovascular hypertension, together with physiologic and pathologic studies in a series of over 80 patients treated by direct renal revascularization. The surgical technics for correcting this form of hypertension will be presented.
(Booth S-13)

Some Properties of Tham, An Amine Buffer of Low Toxicity. *G. G. Nahas. H. C. Slocum, and E. C. Jordan, Washington, D. C.*

This exhibit illustrates the physicochemical properties, the physiologic and pharmacologic activities and toxicity of tris(hydroxymethyl)aminomethane. This amine buffer is now undergoing, in a large number of areas, clinical tests for the control of respiratory and metabolic acidosis. Its use in cardiac patients when sodium buffers are not indicated is also being studied.
(Booth S-29)

Cardiovascular Manifestations of Abnormal Potassium States. *Jack Sanders and Jack Martt, Columbia, Mo.*

This is a graphic illustration of the manifestations of potassium upon the human cardiovascular system. Diagrams illustrating the clinical situations and mechanisms predisposing to potassium disturbances are shown. Examples of the electrocardiographic manifestations of potassium disturbances and the response to therapy are illustrated.

(Booth S-30)

Further Observations on Studies of Biogenic Amines in Animals and Man. *Arthur L. Scherbel and Victor G. deWolfe, Cleveland, Ohio*

The relation of serotonin, histamine, catecholamines and related substances to experimental and certain clinical disorders involving the cardiovascular and connective tissue systems in animals and humans is described. Pharmacologic actions and clinical response to compounds that either increase or decrease amine activity are included.

(Booth S-25)

Damages of "Silicone-Like Property" of Vascular Endothelium by Arteriosclerosis Substances and Their Prevention by Nialamide. *Takio Shimamoto, Tokyo, Japan*

Histological slides and tables demonstrating the effect of arteriosclerogenic substances, such as polypeptides, high molecular substances and catecholamines on the vascular endothelium resulting in adherence of platelets and leukocytes and formation of white thrombi, accompanied by decreased clotting time, reduction of circulating platelets and its prevention by nialamide are shown.

(Booth S-9)

Cellular Physiology of Aging: Various Expressions of a Biologic Process. *Nathan Shock and Bernard L. Strehler, Baltimore, Md.*

This exhibit presents the background, present status and current research on the so-called "age pigments" which accumulate in human brain, heart, and other nondividing cells.

(Booth S-33)

Intracavitary Electrode Catheter As An Aid to Cardiac Catheterization. *Gerald I. Shugoll, John H. Mazur, R. J. Pearson, Jr., Bethesda, Md., and Henry R. Cooper, Fort Lauderdale, Fla.*

The exhibit points out the value of the catheter in routine cardiac catheterization as an aid to more accurate diagnosis, as a means of facilitating catheterization by quicker and more accurate localization of the catheter tip, thus reducing fluoroscopy time, and finally as a means of increasing the safety of the procedure by indicating undue pressure of the catheter tip against the endocardium before arrhythmia occurs. Illustrative examples of the normal intracavitary electrocardiogram from various sites in the heart, injury current and specific cases are presented.

(Booth S-23)

Injection Casts of the Microcirculation. *Sidney S. Sobin, Wallace G. Frasher, Barbara Krueckel, and Herta Tremer, Los Angeles, Calif.*

Selected vascular beds are readily and completely filled with a specifically prepared unique inert polymer; subsequent immediate tissue clearing provides stereomicroscopic 3-dimensional pattern of the microcirculation. Capillary beds of lung (alveolus), liver (sinusoid), kidney (glomerulus) and other organs are shown to take on new organizational appearance and significance.

(Booth S-21)

Stenosis of the Semilunar Valves. *Rodman E. Taber, Conrad R. Lam, Edward Green, Ellet Drake, and Robert Ormand, Detroit, Mich.*

This exhibit shows the various diagnostic features of pulmonary valvular and infundibular stenosis, as well as congenital and acquired aortic valve stenosis. The history and physical examination, roentgenograms, electrocardiograms, and catheterization findings will be illustrated. Infundibular stenosis of both the pulmonary and aortic valves is also demonstrated. The various operative procedures which have been found useful in correcting these conditions are presented by various means, including a short motion picture film strip. The results are summarized. A demonstration of the poststenotic thrill and murmur which occurs in some of these conditions is presented. The observer may feel the thrill as well as hear the murmur.

(Booth S-16)

Circulation During Hypotension (Shock). *Max Harry Weil, Robert B. Sudrann, and Daniel O'Sullivan, Los Angeles, Calif.*

Like a city water system, the cardiovascular system consists of reservoirs, conduits, and a pumping station. The physiologic changes controlling the flow of blood through the vascular bed are

quite comparable to the mechanical adjustments that govern the flow of water through a water system. With this analogy in mind, a functioning model of the cardiovascular system has been developed which simulates the human circulation. The model is designed to demonstrate the mechanisms by which seemingly unrelated disease states cause a fall in blood pressure, the hemodynamic disturbances which are clinically recognized as the state of shock.
(Booth S-32)

Microanatomy in Three Dimensions. *T. W. Williams and C. C. Boyer, Morgantown, W. Va.*

Stereophotomacrographs of special preparations of vascular beds and other structural units presented as an aid to understanding morphologic relationships in the zone of anatomy between that seen by the naked eye and that seen in the ordinary microscopic section.
(Booth S-22)

Committee on Professional Education, American Heart Association. *Committee Chairman: Stewart G. Wolf, Jr., Oklahoma City, Okla.*

The Committee on Professional Education has prepared an educational exhibit on auscultation. It gives the physician an opportunity to test his diagnostic ability concerning heart sounds. A series of 15 common conditions, sufficiently typical to be diagnosed by auscultation alone, is presented. The recordings are on tape and are played back through individual stethophones, while the visual pattern can be followed simultaneously on large oscilloscopes. The physician will be able to check his own results in listening to a parallel series of these 15 conditions giving the exact auscultatory diagnosis. The exhibit will include a selection of the Association's publications and teaching aids, and public educational materials which physicians may wish to review for possible use with their patients.
(Booth S-11)

INDUSTRIAL EXHIBITS

All Exhibits will be Displayed in Kiel Auditorium

Advanced Instruments, Inc., Newton Highlands, Mass. (Booth 42). *For ultraprecise 0.002pH, the new Vibron pH Electrometer; electrodes for anaerobic blood, and, if ready pCO_2 and Na^+. For precise Na^+ and K^+, the new, high-stability Advanced Flame Photometer, smallest instrument, featuring big-instrument repeatability. For precise osmolarity, the proven, widely-used, direct-reading Fiske Osmometer, ± mOsm repeatability. Sample sizes down to 0.2 ml.*

Armour Pharmaceutical Company, Chicago, Ill. (Booth 11) *will include Arcofac, for reduction of blood cholesterol levels; Pentritol Tempules, which release 30 mg. of pentaerythritol tetranitrate in 3 divided doses to provide 12-hour relief in angina pectoris; and Chymoral, a new systemic anti-inflammatory enzyme tablet which reduces inflammation, swelling and pain in numerous conditions including thrombophlebitis.*

C. R. Bard, Inc., Summit, N. J. (Booth 27) *will feature Teflon Knitted and Woven Arterial Grafts, Teflon Interlocking Mesh for tissue repair, Cardiovascular and Venous Catheters and Bardic Intracath.*

Becton, Dickinson and Company, Rutherford, N. J. (Booth 57) *cordially invite you to visit their exhibit of special B-D products for heart catheterization and heart surgery. Among the items displayed will be rotating adapters, stopcocks, animal tested medical grade vinyl, polyethylene tubing (sterile and disposable), and the specially designed needles by medical specialists.*

Birtcher Corporation, Los Angeles, Calif. (Booth 38) *features their newest line of electronic cardiac instruments comprising a complete Mobile Cardiac Monitoring and Resuscitation Center. A Cardioscope, Electrocardiograph, EEG Pre-Amplifier, Electronic Switch, Defibrillator and portable Heartpacer are mounted on a 5′ Mobile Cabinet, which also provides capacious storage for additional items necessary to facilitate resuscitative procedures.*

Blakiston Division of McGraw-Hill Book Co., New York, N. Y. (Booth 18) *will feature: Luisada and Rosa's Treatment of Cardiovascular Emergencies; Luisada's Cardiology: An Encyclopedia of the Cardiovascular System, 4 volumes; Hoffman and Cranefield's Electrophysiology of the Heart; Blum's The Management of the Doctor-Patient Relationship; Innerfield's Enzymes in Clinical Medicine; Kassay's Clinical Applications of Bronchology; Stanbury Wyngaarden, and Fredrickson's The Metabolic Basis of Inherited Disease; Flach and Regan's Chemotherapy in Emotional Disorders.*

Bowen & Company, Inc., Bethesda, Md. (Booth 72) *will feature Welsh Electrodes, Krasno-Graybiel Plastrodes, Ballistocardiograph, QT Calculator and Alcohol Dispenser. Representatives will be glad to give complete information on this equipment and discuss your requirements.*

Burdick Corporation, Milton, Wis. (Booth 29) *will exhibit their line of modern electrocardiographic equipment. A feature of especial interest will be their new console model, mounted on large easy rolling casters, with ample drawer and working space for mobile operation. Doctors are invited to visit the exhibit to see the new features of their equipment.*

Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N. Y. (Booth 45). *Extensive research facilities have long been active in the field of cardiovascular diseases. The latest information will be available on their pure digitalis glycoside, Lanoxin brand Digoxin, and antianginal agent, Cardilate brand Erythrol Tetranitrate, as well as any new drug development completed at the date of this meeting.*

Burton, Parsons & Company, Washington, D. C. (Booth 65). *Information, samples and literature will be available for their EKG Sol, the electrode cream for electrocardiography and electroencephalography, along with their original bulk preparations, Konsyl and L. A. Formula. L. A. Formula contains 50 per cent bulk-producing material dispersed in an equal amount of lactose and dextrose. Konsyl, on the other hand, contains 100 per cent bulk-producing material and is a product intended for the obese, the diabetic, and others with restricted caloric diets.*

Cambridge Instrument Company, Inc., New York, N. Y. (Booths 31 and 32) *will exhibit Multi-Channel Units for recording and monitoring various physiologic and biophysical phenomena; their*

ersa-Scribe, the versatile portable Electrocar-iograph; explosion-proof operating room Car-ioscope used in the operating room and in onitoring experimental phenomena (with re-otely-operated Simpli-Scribe Direct-Writing ortable Electrocardiograph); Audio Visual eart Sound Recorder used in the study and aching of auscultation; Research pH Meter; ulmonary Function Tester; Gamma Ray Pock- Dosimeters; Dye Dilution Recorder. Engi-eers will be glad to give complete information nd discuss any instrumentation requirements.

Ca nation Company, Los Angeles, Calif. (Booth 23). *Medical specialists will be pleased to present ecent literature and information regarding their nstant Non-Fat Milk. Any questions pertain-ng to their physician-researched material for use n your practice or hospital will be gladly dis-cussed.*

Ciba Pharmaceutical Products Inc., Summit, N. J. (Booth 25). *Ismelin, their new antihypertensive indicated in advancing hypertension. Alone, or in combination, it has lowered blood pressure effectively in 80 to 90 per cent of patients. It affords a new way to control hypertension. Since it acts at the site of arteriolar blood pressure regulation, that is, the nerve-arteriole junction, it has no central or parasympathetic effects. Representatives will be glad to discuss this and their other products.*

Coca-Cola Company, Atlanta, Ga. (Special Area). *Ice-cold Coca-Cola served through the courtesy and cooperation of the Coca-Cola Bottling Company of St. Louis and the Coca-Cola Company.*

Corco Incorporated, Culver City, Calif. (Booth 15). *Two models of the completely autoclavable Kay-Anderson Heart-Lung, featuring the automatic filmer, are now joined by a unique and extremely efficient Heat Exchanger. Also on display will be an Ultrasonic Cleaner, which assures the ultimate in cleanliness and was specifically designed for cleaning the heart-lung machine.*

Cor s Corporation, Miami, Fla. (Booth 81). *The recalative Angiograph, used to obtain high olution, high contrast angiograms, utilizing ll dosages of radio-opaque dye and generally ilable x-ray equipment will be shown. Also display will be an Automatic Alternating rniquet employed to restrict alternately, in iform fashion, venous return from the limbs, eby alleviating acute pulmonary congestion.*

Corn Products Company and the Best Foods Division, New York, N. Y. (Booth 58) *will have a joint display of their products. Representatives look forward to welcoming you to their exhibit.*

Custom Engineering and Development Company, St. Louis, Mo. (Booth 75). *A Hypothermia Apparatus consisting of 2 completely automatic reservoir-pumping systems, together with an efficient heat exchanger and associated equipment. A new Gibbon-Mayo Pump-Oxygenator, which has been reduced to less than one-half the size of its predecessor but still retains the advantages of the larger machine. A new Coronary Sinus Sucker system, developed by International Business Machines Corporation in cooperation with the Mayo Clinic. This apparatus provides improved coronary sinus blood handling with any pump-oxygenator.*

Dallons Laboratories, Inc., Los Angeles, Calif. (Booth 14) *will display and demonstrate the latest advanced line of electronic instrumentation for cardiovascular diagnosis and surgery. Their Telco Micromanometers provide simultaneous sound and pressure recordings, and oscilloscope visualization, and apparatus for simultaneous right and left catheterization. You are cordially invited to visit their exhibit.*

Davies, Rose & Company, Ltd., Boston, Mass. (Booth 74) *will feature Pil. Digitalis and Tablets Quinidine Sulfate (Natural). Their representatives will be on hand to welcome you and to explain the dependability of their laboratory productions.*

F. A. Davis Company, Philadelphia, Pa. (Booth 72) *will feature the new Differential Diagnosis of the Electrocardiogram by Arbeit, Rubin and Gross, a most helpful consultant to expedite an exact ECG diagnosis. Other timely books are Stroud's Cardiovascular Disease, now in loose-leaf form, Page's Arterial Hypertension, and Mendelson's Cardiac Disease in Pregnancy.*

Electrodyne Company, Inc., Norwood, Mass. (Booth 46). *Instruments for closed-chest prevention, detection, and treatment of cardiac standstill and ventricular fibrillation. Featured will be their Miniature All-Transistor Pacemaker, Model TR-3, operated on battery or standard AC outlet. Currents for both external and direct stimulation of the heart are available. Also featured will be their PM-65 with Electrocardioscope which monitors cardiac activity and automatically provides effective external stimulation of the dormant heart at the very onset of cardiac arrest.*

Electronics for Medicine, Inc., White Plains, N. Y. (Booths 33-34). *Cathode ray monitoring and recording systems for 8-channel operation. A new 4-channel assembly for both scalar and loop (X-Y) recording with a built-in camera. A 2- or 4-channel tape system for simultaneous recording of the phonocardiogram, ECG or pressures. Portable monitors for ECG/EEG or pressures.*

Endo Laboratories Inc., Richmond Hill, N. Y. (Booth 56) *presents the following therapeutic preparations: Coumadin, the original Warfarin Sodium responsible for establishing this drug as the best anticoagulant available today. Numorphan, l-14 hydroxydihydromorphinone, the analgesic with wide clinical acceptance.*

Ensco, Incorporated, Salt Lake City, Utah (Booth 7) *will display their line of cardiovascular research and diagnosis equipment. The exhibit includes a Monitoring System for use in research, diagnosis, and surgical monitoring. It will include an electronically controlled injector and a constant rate syringe puller for dye dilution studies and an oximeter amplifier for oximetry and dye recording.*

Foregger Company, Inc., Roslyn Heights, N. Y. (Booth 67) *will exhibit their Pulspirator, the new pump oxygenator which does not require the use of freshly drawn or specially prepared donor blood. Completely portable and requiring no electricity, the Pulspirator is remarkably economical in the use of ordinary ACD blood. Patients' total requirements have averaged 3 pints during thoracotomy, perfusion and postoperatively.*

E. Fougera & Co., Inc., Hicksville, N. Y. (Booth 21) *features the extensive clinical background and professional acceptance of Digitaline Nativelle, the original purified glycoside of Digitalis. Time tested dependability and broad range of dose forms make Digitaline Nativelle a reliable drug for management of the failing heart. New clinical information on Diasal in the management of cardiovascular and associated conditions will also be featured.*

Geigy Pharmaceuticals, Yonkers, N. Y. (Booth 63) *cordially invites you to visit their technical display. Their original contributions to modern therapy of cardiovascular, rheumatic, psychiatric and metabolic disorders will be presented by representatives in attendance.*

General Diagnostics Division of Warner-Chilcott Labs., Morris Plains, N. J. (Booth 68) *will feature Simplastin: a pre-extracted thromboplastin-calcium, rigidly standardized to give consistent reproducible results from vial to vial and lot to lot. Available in 6-determination and 20-determination vials. Diagnostic Plasma: for prothrombin time control. A normal plasma which reacts like a pool of normal plasmas, eliminating individual variability. Rigidly standardized, reliable and accurate. Urograph: a paper chromatography technic for urea nitrogen determinations, quantitative, yet simple and accurate.*

General Foods Kitchens, White Plains, N. Y. (Booths 61 and 62). *Enjoy a cup of Sanka Coffee . . . real coffee, with 97 per cent of the caffein removed. You will find it delicious coffee, made in the cup or family style and for patients, too, when they need less caffein. Register for an office supply of our leaflet on caffein.*

Gilford Instrument Laboratories Inc., Oberlin, Ohio (Booth 20) *will exhibit a group of instruments for cardiopulmonary research and diagnosis. Among these will be their well-known Cuvette Densitometer/Oximeter, Linear Digital Cardiotachometer, Computing Spirometer, and Blood Pressure Recorder. A new attachment of the Spirometer will be demonstrated which permits direct measurement of maximum expiratory flow rate and midexpiratory flow without recording. A new attachment for spectrophotometers, which records optical density continuously for rapid enzyme assays, will also be shown.*

Grune & Stratton, Inc., New York, N. Y. (Booth 48) *will show their newest volumes. Included will be such books as Master and Donoso's Visual Aid in Cardiologic Diagnosis and Treatment; Heart Sounds and Murmurs by Ongley, et al.; Gordon's Clinical Cardiopulmonary Physiology; Schnitzer's Electrocardiographic Technique; Butterworth's Cardiac Auscultation; as well as their outstanding journal, Progress in Cardiovascular Diseases.*

Hiss Pharmacal Co., Inc., Utica, N. Y. (Booth 3) *will feature Vasotrate Unicelles, 30 mg., 80 mg., nos. 1 and 2, for the prevention of recurrent angina attacks; Tenamine Unicelles, for the treatment of hypertension and as a mild tranquilizer; and Liparin Injection, used in diseases associated with impaired lipid metabolism. Representatives will be at the booth to service the physicians.*

Paul B. Hoeber, Inc., New York, N. Y. (Booth 66). *Among the new books on display are Warshaw's The Heart in Industry; Rosenbaum & Belknap's*

Work and the Heart; and Durham's The Encyclopedia of Medical Syndromes. Also of particular interest are Plotz' Coronary Heart Disease; Bayley's Electrocardiographic Analysis, and Gardberg's Clinical Electrocardiography. Their representative will be glad to help you.

Info-Dex Heart Registry System, Medical Case History Bureau, New York, N. Y. (Booth 79) *will show the just released Info-Dex Heart Registry. It is simple and compact, and is invaluable for research and special studies on cardiovascular diseases.*

Instrumentation Associates, Inc., New York, N. Y. (Booth 70). *A selection of cardiopulmonary equipment, Pulmonet for lung volumes, Compliance Unit, Spirometers, Pneumotachographs, Rapid Gas Analysis for O_2, CO_2, He, using Thermal conductivity Infra-red Gas Analysers CO_2, CO. Also on display is the Bird Respirator with positive and negative phase and automatic cycling.*

Ives-Cameron Company, New York, N. Y. (Booth 9) *cordially invites you to stop at their booth where Isordil, a new, long-acting coronary vasodilator, will be featured. Isordil is offered for the therapeutic and prophylactic management of angina pectoris. Also featured will be Cyclospasmol, a new peripheral vasodilator. Cyclospasmol is offered for the treatment of peripheral vascular diseases.*

Keleket X-Ray Corporation, Waltham, Mass. (Booth 8) *will feature a complete heart catheterization system including 9" image intensifier with television and cine attachments, plus heart catheterization table. Representatives will be glad to give complete information on this equipment and discuss your requirements.*

Thos. Leeming & Co., Inc., New York, N. Y. (Booth 13). *A significant report on a long-term controlled study of Clarin (sublingual heparin) and its effect on the incidence of recurrent myocardial infarction is now available (together with data on Clarin's ability to lower postprandial serum lipid levels). Information on the potent coronary vasodilator, Metamine Sustained, and its use in coronary insufficiency will also be available.*

Eli Lilly and Company, Indianapolis, Ind. (Booths 39 and 40). *You are cordially invited to visit their exhibit where sales people in attendance will welcome your questions about their products and recent therapeutic developments.*

Maico Electronics, Inc., Minneapolis, Minn. (Booth 10), *a pioneer hearing research firm, will demonstrate the latest improved model of their popular electronic amplified stethoscope, the Stethetron. The instrument permits accurate selective amplification of a widely divergent range of body sounds.*

Mallinckrodt Chemical Works, St. Louis, Mo. (Booth 78). *Ditriokon, a well tolerated contrast material, which has certain advantages over other products in that it can be given rapidly with ease in less than 2 seconds, in amounts of 50 cc. or less. It has a low viscosity and gives excellent shadows, equal in opacity to any of the products presently used for angiocardiography.*

Medtronic, Inc., Minneapolis, Minn. (Booth 77) *will exhibit the latest developments in electronic instruments to serve the cardiologist and cardiovascular surgeon. These instruments include their miniature transistor Cardiac Pacemaker, Cardiac Monitors, Cardiac Resuscitator, Cardiac Sentinel, Electrocardiosync, Cardiac Tachograph, and the Cardiac Defibrillator available for internal or external application.*

Merck Sharp & Dohme, West Point, Pa. (Booths 35 and 36). *Diuril and HydroDiuril, orally effective, nonmercurial diuretic-antihypertensive agents are featured. Technically trained personnel will be present to discuss these and other subjects of clinical interest.*

Wm. S. Merrell Company, Cincinnati, Ohio (Booths 4 and 5). *MER/29, for control of the excess production of cholesterol within the body. It is now possible to reduce both serum and tissue cholesterol levels with 1 small capsule daily. Representatives in attendance will be happy to inform you of the latest clinical reports on this significant product.*

Micro X-Ray Recorder, Inc., Chicago, Ill. (Booth 43). *Over 50 series of 2" × 2" medical teaching slides on various subjects, including 18 on the heart and chest, compiled from the files of leading specialists and institutions are featured. These will be available for viewing on their Recorder Projector-Viewer. This unit will project 2" × 2" slides and 35 mm. film for teaching and lecture without burning or buckling even cardboard-mounted slides.*

C. V. Mosby Company, St. Louis, Mo. (Booth 55). *New knowledge, ideas, research and technic: all are waiting for you in their newest books for 1959 and 1960. Look over these books at your leisure and convenience; if you wish assistance,*

their representative will be happy to discuss any book with you.

North American Philips Co., Inc., New York, N. Y. (Booth 49) *offers a complete Angiocardiographic Installation with a variety of the newest Generators, TV Systems, and Cine Systems for coronary arteriography and congenital heart diagnosis.*

Ortho Pharmaceutical Corporation, Raritan, N. J. (Booth 19). *Representatives are exhibiting Actase Fibrinolysin (Human), the first blood clot lysing agent in its field. Literature discussing its use in a variety of clinical indications is available. In addition, scientists from their Research Foundation will be on hand to answer questions regarding the use of fibrinolytic therapy in medical practice.*

Riker Laboratories, Inc., Northridge, Calif. (Booth 64). *LH 400 (Lipo-Hepin), sodium heparin U.S.P., 400 mg. per cc., allows a significant increase in efficiency of anticoagulant and lipoprotein lipase response. Administration and control problems usually associated with heparin therapy are essentially eliminated. A representative will be present to answer questions relative to anticoagulant and lipoprotein lipase (postheparin) enzyme therapy.*

Roche Laboratories, Nutley, N. J. (Booths 16 and 17) *will feature new Librium, which has rapid and often dramatic therapeutic effects in anxiety and tension as well as certain types of depression. Librium is free from autonomic or extrapyramidal side effects and is remarkably safe over a wide dosage range. Marplan, a new amine oxidase regulator, is also presented.*

Sanborn Company, Waltham, Mass. (Booths 53 and 54). *A wide selection of instruments for biophysical research will be on display: some in simulated operation, to aid understanding of function and operating features. Their equipment includes Recording Systems (single and multichannel, direct-writing, photographic and tape), Monitoring Oscilloscopes, Transducers (pressures, temperature, etc.) and new Preamplifiers, permitting a wide range of physiologic applications.*

Sandoz Pharmaceuticals, Hanover, N. J. (Booth 28) *will feature Acylanid acetyldigitoxin, a pure glycoside providing efficient and safe oral digitalis therapy. It is characterized by high absorption, short latency period and good margin of safety. Plexonal: a preferred daytime sedative-relaxant. Cedilanid-D: pure glycoside (Deslanoside, U.S.P. XV) of digitalis lanata with quick onset of action, quick excretion and low toxicity. Useful for i.v. administration in cardiac emergencies and for rapid digitalization.*

W. B. Saunders Company, Philadelphia, Pa. (Booth 2). *A full line of clinical books of up-to-date usefulness will be on display.*

Schering Corporation, Union, N. J. (Booth 6) *takes pleasure in inviting you to visit their exhibit. Several representatives will be there to discuss all aspects of their products such as: Miradon, the new oral anticoagulant with predictable control proved by 5 years' pre-introductory clinical experience and Naqua, effective new oral diuretic and antihypertensive.*

Schick X-Ray Co., Inc., Dis. for Elema-Schoenander AB, Chicago, Ill. (Booth 1). *Their line of equipment includes x-ray and electromedical units; direct-writing jet recorders for ECG, phonocardiography, pressure, etc. Film changers for angiocardiography, high-pressure injection syringes, fluoroscopic tables for catheterization, etc.*

Schwarzer Company, Watertown, Mass. (Booth 73) *presents and demonstrates some of their Cardioscript models, the multipurpose direct-writing instruments for recordings of phonocardiograms (up to 3,000 c.p.s. in 6 selective filters), EKG, EEG, pulse tracings, pressures, oximetry, polarography, dye dilution measurements, ballisto- and vectorcardiograms, blood flow estimations, etc. Also shown are the portable Cardioscript III, and various transducers.*

G. D. Searle & Co., Chicago, Ill. (Booth 41). *You are cordially invited to visit their booth, where representatives will be happy to answer any questions regarding their products of research. Featured will be Aldactone, their new aldosterone-blocking agent for edema or ascites.*

E. R. Squibb & Sons, New York, N. Y. (Booth 30) *has long been a leader in development of new therapeutic agents for prevention and treatment of disease. The results of their diligent research are available to the medical profession in new products or improvements in products already marketed. Representatives will be pleased to present up-to-date information on these advances.*

Statham Instruments, Inc., Hato Rey, Puerto Rico (Booth 24). *The widely used line of physiologic transducers, designed especially for the cardiolo-*

gist and based on the reliable unbonded strain-gage principle, will be shown, with the latest developments featured. Engineering personnel will be present to discuss the selection of optimum types for either clinical, research or instructional applications.

S. Catheter & Instrument Corp., Glens Falls, N. Y. (Booth 26). *Specialist in the manufacture of cardiac catheters, electrodes and tubings, and of a complete line of woven and knitted Teflon prostheses. Research engineers, well versed in design and production of cardiac catheters, will discuss problems, ideas, new developments, etc., at their booth.*

Walker Laboratories, Mount Vernon, N. Y. (Booth 52) *will feature their new Nicalex (Aluminum Nicotinate). Nicalex is a newly synthesized salt of nicotinic acid for the reduction of blood cholesterol. Nicalex may reduce cholesterol levels as much as 200 mg. per cent with no flushing, itching, or G. I. disturbance in over 80 per cent of patients, and with no dietary restrictions.*

Wallace Laboratories, New Brunswick, N. J. (Booths 59 and 60) *representatives will be glad to discuss their drug Miltrate. The drug consists of the tranquilizer meprobamate plus pentaerythritol tetranitrate for effective coronary vasodilation, along with the calming effect of Miltown. It has been proven safe for long-term use.*

Warner-Chilcott Laboratories, Morris Plains, N. J. (Booth 69). *Peritrate, a long-acting coronary vasodilator with no significant change in blood pressure or pulse rate, is presented. Smooth onset of action virtually eliminates nitrate headache. Nardil, a new rapidly effective treatment for depression is also featured. Representatives will be glad to discuss their products with you.*

Waters Corporation, Rochester, Minn. (Booth 71) *will feature almost all new improved models this year, including a linear, less expensive blood densitometer for green dye dilution curves; also new linear, extra-wide range cardiotachometer; redesigned ear oximeter; a nitrogen gas analyzer with remote sampling head; also recording thermistor with unique probes.*

Wesson Oil, New Orleans, La. (Booth 80). *Exhibit will consist of a gas chromatograph, showing the composition of cottonseed oil, shortening and lard with a descriptive text and research findings. Representatives will be glad to answer and discuss any questions you may have.*

Winthrop Laboratories, New York, N. Y. (Booth 47). *Levophed, the natural antishock pressor hormone for patients in severe shock due to myocardial infarction. Levophed raises blood pressure within seconds. Unlike other agents, it also produces an increase in coronary blood flow and enhances oxygen supply to the myocardium.*

Wyeth Laboratories, Philadelphia, Pa. (Booths 37 and 44). *Equanitrate, for angina pectoris prophylaxis, provides prolonged coronary vasodilatation, controls apprehension, anxiety and tension, reducing number and severity of anginal attacks, and increasing exercise tolerance. Ostensin, oral ganglionic-blocking agent for diastolic hypertension management, provides prompt, prolonged hypotensive action with fewer by-effects. With chlorothiazide, Ostensin provides the keystone for effective antihypertensive regimen.*

Wynn Pharmacal Corporation, Philadelphia, Pa. (Booth 76). *Information and samples will be available on Quinaglute Dura-Tab S.M., the only oral Sustained Medication Quinidine Gluconate. Quinidine gluconate has been found to be better absorbed and tolerated than quinidine sulfate. Each dose of Quinaglute maintains uniform plasma levels up to 12 hours. Indicated in cardiac arrhythmias, such as premature contractions, auricular tachycardia, flutter, fibrillation. Also available will be samples on Dura-Tab S.M. aminophylline, sustained medication aminophylline tablets.*

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Index

Abarquez, R. F., 704, 714
Abbott, O. A., 703
Abelmann, W. H., 701, 717, 765, 778
Achor, R. W. P., 702, 710, 722, 816, 820
Adam, M., 711, 714
Adam, W. S., 787
Adams, W. R., 705
Adamson, W. B., 715
Adlersberg, D., 805
Adolph, R. J., 715
Ahumada, J., 807
Agnew, C. H., 837
Agress, C. M., 837
Agustsson, M. H., 699, 704, 715, 717, 794
Aldinger, E. E., 824
Alexson, C. G., 716
Allen, D. F., 775
Allen, E. V., 702, 705
Allenstein, B. J., 716
Allison, R. B., 701, 717
Al-Naaman, Y. D., 711
Alvarez, H., Jr., 837
Alvarez, S., 724
Amer, N. S., 704, 719
American Association of Blood Banks, 837
Anast, C., 784
Anday, I., 731
Anderson, D. L., 824
Anderson, R. M., 711, 770, 839
Andreae, R. L., 764
Andrus, E. C., 703
Anlyan, W. G., 837
Archer, M., 799
Arcilla, R. A., 704, 717, 752
Armer, R. M., 782
Artymowska, C., 817
Assali, N. S., 701, 718
Auchincloss, J. H., Jr., 718
Auld, P. A. M., 802
Ayres, S. M., 718

Bacos, J. M., 719
Baffes, T. G., 705, 795, 839
Bagdonas, A. A., 704, 711, 719, 762, 819
Bahamondes, L., 807
Bahnson, H. T., 705, 816
Bailey, C. P., 703, 719, 777
Baird, B., 699, 720
Baker, B. M., 801
Ballantine, H. T., 737
Ballinger, W. F., II, 711, 720
Baker, N. W., 710, 722
Barnett, G. O., 704, 751
Barrow, J. G., 720
Barry, J., 701, 744
Barry, W. F., 708, 787
Bartolucci, G., 741, 785
Barwinsky, J., 734
Bassingthwaighte, J. B., 721
Battersby, E. J., 721
Bellet, S., 721, 722, 724, 740, 743, 771, 825
Bellet, S. S., 702
Bender, I. B., 712
Bender, S. R., 710, 780
Bendersky, G., 722
Berge, K. G., 710, 722
Bergeron, R. M., 736
Berkowitz, D., 701, 723
Berkson, D. M., 709, 817
Berliner, K., 723
Berman, L., 748
Berman, R., 702
Bernstein, A., 802
Bernstein, S., 711
Bernstein, S. H., 699, 724, 819
Bernstein, W. H., 701, 811
Best, M. M., 698, 724
Beyda, E. J., 724
Bicoff, J. P., 717
Bigelow, W. G., 711
Bihler, L., 826
Bing, R., 698
Bing, R. J., 701, 703, 798
Bishop, L. F., 702
Blackburn, H., 709, 822
Blackburn, H. W., 699, 812, 822
Blair, E., 725
Blake, D. F., 710, 831
Blake, T. M., 791
Blanco, G., 792
Bland, E. F., 829
Blanding, J. D., Jr., 837
Blankenhorn, D. H., 701, 725, 726, 830
Blaustein, A. U., 726
Bleiler, R., 701, 735
Bliss, H. A., 715
Bloomer, W. E., 770, 839
Blumenthal, S., 700, 726, 826
Blumgart, H. L., 702, 727
Bogdonoff, M., 746
Bogdonoff, M. D., 699, 772
Booth, R. W., 706, 727, 834
Borrero, J., 780
Bower, R., 812, 838
Bowers, D., 727
Boyer, C. C., 841
Bradley, S. E., 706, 713
Bradess, V. A., 702, 816
Brandenburg, J. T., 710, 816
Braunwald, E., 699, 703, 704, 710, 728, 751, 752
Breihahn, R. L., 699, 789
Breneman, G. M., 739
Brest, A. N., 706, 728, 780, 791, 837
Briggs, D. I., 710, 835
Brinkhous, K. H., 702
Brockenbrough, E. C., 699, 728
Brodsky, M. B., 807
Brody, D. A., 704, 746, 747
Brown, T. E., 831
Browne, M. J., 706, 755
Brownell, K. D., 700
Brozek, J., 699, 822
Bruce, R. A., 698, 703
Brunson, J. G., 734
Brust, A. A., 700
Bryant, M. F., 729
Burch, G. E., 698, 703
Burchell, H. B., 699, 702, 792, 806
Burke, J. F., 805
Burke, N. B., 785
Butterworth, J. S., 703

Caceres, C. A., 729, 824

C[illegible]tayud, J., 729
C[illegible]iva, F. S., 730
C[illegible]leja, H. B., 730
C[illegible]apbell, W. G., 745
C[illegible]apeti, F. L., 730
C[illegible]apione, K. M., 731
C[illegible]bery, W. J., 824
C[illegible]leton, R. A., 778
C[illegible]twright, R. S., 731
C[illegible]e, R. B., 708, 731, 758
C[illegible]vusoglu, M., 817
Chaffee, W., 733
Chamberlain, B., 730
Chamberlain, F. L., 703, 712
Chandler, A. B., 732
Chardack, W. M., 732
Chasis, H., 705
Cheng, T. O., 732
Chobanian, A. V., 707, 733, 764
Chodos, R. B., 733
Christensen, N. A., 710, 722
Chu, Y. C., 817
Claire, A., 712
Clifton, E. E., 702, 837
Clowes, G. H. A., Jr., 734
Coe, M. H., 712
Coggin, C. J., 705, 734
Cohen, M. E., 737
Coleman, S. L., 799
Collins, K., 734
Committee on Professional Education, A. H. A., 841
Conn, J. W., 704
Connell, W. F., 735, 786
Connor, C. A. R., 703
Connor, W. E., 701, 735
Conway, J., 735
Cook, S. F., 699, 720
Cook, W. L., 709, 735
C[illegible]oley, D. A., 705, 708, 711, 738, 791, 839
C[illegible]per, E. E., 736
C[illegible]per, H. R., 840
C[illegible]rday, E., 701, 702, 736, 766, 838
C[illegible]rrado, M. A., 700
C[illegible]by, M. M., 762
C[illegible]sby, R. S., 736, 762
C[illegible]vley, R. A., 725
C[illegible]ige, E., 760
Crane, C., 708, 743
Crawford, E. S., 705, 708, 711, 738, 791, 839
Crawford, T. I., 838
Crawley, M., 712
Crevasse, L., 737
Creech, O., 706
Croll, M. N., 701, 723
Cross, F. S., 838
Cruickshank, B., 776
Cuddy, R., 701, 744, 813
Currens, J. H., 737

Dack, S., 703
Damato, A. N., 752
Dammann, J. F., Jr., 823
Danese, C., 706, 738, 812, 838
Danforth, W. H., 703
Danhof, I. E., 711, 714
Daniell, M. B., 761
Davila, J. C., 738
Davis, C. S., 759
Davis, L. D., 710, 835
Davis, M. B., 790
Davis, M. V., 711, 714
Dawber, T. R., 709
Day, S. B., 703
Deaton, H. L., 837
De Bakey, M. E., 702, 705, 708, 711, 738, 761, 791, 839
Debbas, J. N., 838
De Boer, A., 839
de Castro, E. G., 766
deGroot, W. J., 700, 739, 794, 799
de Gubareff, T., 826
De Jesus, J. R., Jr., 739
Del Guercio, L. R. M., 734
deMaine, M. M., 806
De Mesquita, Q. H., 777
Demetz, A., 801
Derrick, J. R., 740, 837
Desposito, F., 819
Devlin, L. P., 785
deWolfe, V. G., 840
Dexter, L., 703, 706, 743
Deykin, D., 701, 740
Di Bartolo, G., 782
Dickstein, E. R., 740, 743, 771
Dillon, M. L., 711, 750
Dimond, E. G., 698, 703
Donahue, W. C., 706, 743
Dodge, H. T., 741
Drake, E., 840
Dreifus, L. S., 705, 710, 741, 780, 797
Duchesne, E. R., 830
Duncan, C. H., 698, 724
Dunne, E. F., 711, 839
DuShane, J. W., 699, 706, 721, 792, 806
Dustan, H., 741
Dustan, H. P., 707
Dykstra, P. C., 711

Eagan, J. T., 704, 719, 742
Earle, D. P., 731
Eastman, G., 742
Eckstein, J. W., 704, 742, 747
Eckstein, R. W., 708, 790
Edelman, J., 743
Edmands, R. E., 720
Edwards, A. E., 738
Edwards, E. A., 706, 708, 743
Edwards, J. E., 699, 702, 710, 792, 806, 816, 820
Edwards, W. S., 744
Eggers, G. W. N., Jr., 700, 794
Ehrenhaft, J. L., 702
Eich, R., 701, 744, 813
Ellestad, M., 782
Ellis, L. B., 701, 717, 744
Engelberg, H., 699, 745
Engle, M. A., 745, 756
Engler, H. S., 838
Erb, B. D., 704, 746, 747
Ernstene, A. C., 698
Esmond, W. G., 725
Esterly, J. R., 834
Estes, E. H., 699, 772
Estes, E. H., Jr., 746
Evans, J. A., 818
Evans, J. W., 704, 746, 747
Evans, T., 741
Eyler, W., 837

Fabrizio, A. M., 825

Feinberg, H., 708, 774
Feinberg, L. J., 740, 771, 825
Feinstein, A. R., 699, 747, 821
Feisal, K. A., 747
Fell, E. H., 715, 813
Fields, L. G., 837
Finby, N., 756
Finlayson, J. K., 707, 835
Finnerty, F. A., Jr., 748, 825
Fisch, C., 749
Fischel, E., 700
Fisher, D. L., 699, 749
Fisher, J. M., 700, 749,
Fishman, A. P., 700, 706, 708, 826
Fishman, I. W., 708, 771
Fletcher, A., 702
Floyd, W. L., 711, 750, 793
Foley, W. T., 838
Forbes, A. L., 750
Forkner, C. E., Jr., 704, 706, 765, 818
Forster, R. E., 708
Foster, J. E., 709, 711
Foulkes, E. C., 710, 750
Fowler, N. O., 751, 807
Fowler, W. S., 708
Fox, S. M., III, 704, 751
Frahm, C. J., 710, 728, 751
Francis, W. W., 759
Frank, M. J., 701, 798
Frasher, W. G., 840
Frazier, L. E., 699, 833
Freiman, A. H., 704, 714, 824
Freis, E. D., 702, 706, 752
Fremont-Smith, P., 699, 789
Friedberg, C. K., 775
Friedberg, S. J., 746, 803
Friedman, I. A., 813
Fritz, A. J., 738
Frommer, P. L., 704, 752
Fry, D. L., 704, 751
Fujiy, H., 723
Fyler, D. C., 818

Gabrieli, E. R., 838
Gage, A. A., 732
Gantt, J., 704, 766
Garabedian, G. H., 781
Garnier, B., 723
Gasul, B. M., 699, 702, 704, 715, 717, 752, 794, 813
Gearing, F. R., 753
Gelb, I. J., 809
Georgopoulos, A. J., 704, 753
Gerbode, F., 706, 711, 753, 754
Gerbode, F. L., 705
Gerein, A. N., 838
Gertler, M. M., 710, 754
Giannelli, S., Jr., 754
Gibbons, J. E., 755
Gibson, W., 727
Gifford, R. W., Jr., 707, 755
Gilbert, R., 718
Gilkinson, J. I., 712
Gilmore, B. L., 752
Gipe, F., 712
Gitlow, S. E., 707, 788
Glenn, W. W. L., 705, 706, 709, 755
Glenner, G. G., 721
Glover, R., 702
Glover, R. P., 738, 756, 825
Goetz, K. L., 710, 835
Goldberg, H. P., 745
Goldring, D., 826
Goldring, W., 700
Goldsmith, E. I., 756
Golinko, R. J., 802
Goluboff, B., 793
Goodloe, M. H. R., 720
Gordon, A. J., 757
Gordon, A. S., 757
Gorlin, R., 703, 704, 778, 789, 827
Gorten, R. J., 757
Gousios, A., 809
Grande, F., 707, 788
Grant, R. P., 703
Greatbatch, W., 732
Green, E., 840
Green, E. W., 758
Green, H. D., 709
Greenfield, J. C., Jr., 704, 751
Greenspan, R., 706
Gregg, D. E., 703
Gregory, M., 712
Griffith, G. C., 702, 758
Griffiths, S. P., 700, 726, 826
Griggs, D. E., 806
Griggs, D. M., Jr., 708, 731, 758
Grishman, A., 703
Groom, D., 759
Gross, R. E., 705, 776
Grossi, C. E., 837
Gueron, M., 751, 807
Guidry, J. P., 712
Gunnells, J. C., 757
Gurdjian, E. S., 708
Guz, A., 704, 759, 763

Hackett, P., 725
Hahn, E. S., 707, 767
Hair, T. E., Jr., 759
Hall, Y., 709, 817
Hanlon, C. R., 705, 706, 832
Hankin, J., 712
Harken, D. E., 702, 744
Harkins, G. A., 706, 753, 754
Harman, D., 760
Harmel, M. H., 770
Harned, H. S., Jr., 760
Harris, S. C., 712
Harrison, J. L., 738
Harrison, J. S., 711, 801
Harshaw, D. W., 710, 804
Hartman, J. M., 727
Hauck, A. J., 705, 761, 776, 826
Haywood, L. J., 761, 806
Head, J. M., 838
Head, J. R., 838
Head, L. R., 838
Headley, W. M., 838
Hellems, H. K., 701, 798
Hellerstein, H. K., 703
Helmstetter, B. S., 710, 773
Helwig, J., Jr., 803
Henly, W. S., 708, 738, 761
Henry, R. L., 837
Herman, L. M., 762
Heymans, C., 709
Higginbotham, A. C., 701, 762
Higginbotham, F. H., 701, 762
Higgins, I. T. T., 709
Hirose, T., 777
Hirschhorn, K., 699, 812
Hodges, R. E., 701, 735
Hoffman, B. F., 704, 709, 711, 719, 762, 770, 819

Hoffman, J. I. E., 704, 759, 763
Hohf, R. P., 763
Hollander, W., 707, 733, 764
Holswade, G. R., 745
Hoobler, S. W., 703
Hopkins, W. A., 790
Horan, L. G., 764
Horsley, A. W., 742, 747
Horwitz, O., 701, 765
Hosier, D. M., 706, 730, 812, 834
Howard, H. S., 705, 832
Howard, J. M., 706, 738, 812, 838
Hubert, K., 781
Hudson, T. R., 838
Hufnagel, C., 707
Hufnagel, C. A., 702
Hugenholtz, P. G., 704, 765
Hughes, R. H., 699, 833
Hull, E., 703
Hultgren, H. N., 784
Humphreys, G. H., II, 801
Humphries, A. W., 702
Hyman, A. L., 704, 766
Hyman, E. S., 704, 766

Inderleid, H. F., 792, 839
Irving, D. W., 701, 736, 766, 838
Isaacs, J. P., 708, 820

Jablon, J. M., 804
Jablons, B., 707, 766, 767
Jacobson, J. H., II, 705, 767
Jaffe, H., 736
James, T. N., 701, 767
Jamison, W. L., 803
January, L. E., 698
Jaqier, W., 755
Jenks, S. A., 804
Johns, V. J. Jr., 761
Johnson, B. C., 768
Johnson, E. E., 699, 811
Johnson, J. E., 739
Johnson, J. L., 768
Johnston, J. B., 706, 753, 754
Jolliffe, N., 799
Jones, J. C., 757
Jones, R. J., 710, 773
Jordan, E. C., 839
Judson, W. E., 704, 768

Kaiser, G., 810
Kalmansohn, R. B., 769
Kalmansohn, R. W., 769
Kaplan, D. E., 769
Karis, J. H., 770
Kark, R. M., 704
Karlen, W. S., 802
Karnovsky, M. L., 710
Karsak, N., 801
Katcher, A. H., 804
Katz, L. N., 708, 710, 774, 789
Katznelson, G., 778
Kay, E. B., 705, 711, 770, 836, 839
Kay, J. H., 711, 770, 839
Keith, J., 700
Kellner, A., 701
Kellogg, F., 708, 771, 779
Kendall, F. E., 698
Kennamer, R., 777, 797
Kent, E. M., 779
Kershbaum, A., 771
Kerth, W. J., 753
Keys, J. W., 739
Keys, A., 699, 709, 710, 822
Kezdi, P., 710, 771, 831
King, E. Q., 772
King, R. C., 790
Kinsell, L. W., 710
Kinsey, D., 704, 772
Kirkendall, W. M., 702
Kirschner, P. A., 757
Kistin, A. D., 772
Kistler, J. C., 764
Klatte, E. C., 704, 768, 782
Kleeman, C. R., 707, 785
Klein, R. F., 699, 746, 772
Klepetar, E., 709, 822
Kobernick, J. L., 707, 808
Kohlstaedt, K. G., 703
Kohn, R. M., 773
Kositchek, R. J., 701, 773
Kossmann, C. E., 704
Kozam, R. L., 718
Krueckel, B., 840
Kuhn, P. R., 710, 773
Kuhn, R., 745
Kunin, A. S., 706, 774
Kurland, G. S., 706, 818
Kwapis, B., 712

LaDue, J. S., 698, 704, 714
Lafontant, R., 708, 774
Laird, J., 784
Lalossis, D., 775
Lam, C. R., 705, 739, 821, 840
Lambert, E. C., 706
Langendorf, R., 700, 775, 796
Larson, R., 708, 771
Lasser, J. J., 775
Lasser, R. P., 775
Lazzarini, A., Jr., 776
Lebowitz, W. B., 776
Lee, D. H., 723
Leeds, R. F., 737
Lees, M., 705, 776
Lemmon, W. M., 719, 777
Lendrum, B. L., 752
Leonard, J. J., 700, 739, 794, 799
Leone, M., 779
Lev, M., 706, 708, 777, 839
Levine, H. D., 704, 765
Levine, H. J., 704, 778, 789, 827
Levine, J., 710, 804
Levinson, G. E., 778
Levowitz, B. S., 779
Levy, J. V., 779
Lewis, D. H., 803
Lewis, F. J., 711
Lieberman, J., 779
Lieberman, J. S., 780
Likoff, W. M., 702, 705, 710, 723, 741, 780, 797
Lillehei, C. W., 702, 705, 781
Lim, T. P. K., 731
Lim, W. N., 781
Lindberg, H. A., 709, 817
Linenthal, A. J., 781
Link, K. P., 705
Little, A., 701, 800
Litwak, R. S., 701, 811
Liu, C. K., 708, 771, 782
Logsdon, G. R., 699, 749
Logue, R. B., 709

Long, D. M., Jr., 705, 781
Lord, J. W., Jr., 776
Lovette, J. B., 779
Luft, U. C., 731
Luisada, A. A., 703, 782
Lukas, D. S., 718, 745
Luria, M. N., 707, 835
Lurie, P. R., 782
Lyons, C., 744
Lyons, R., 702, 813

Magee, J. H., 750
Magida, M. G., 783
Magidson, O., 711, 770, 839
Magovern, G. J., 779
Mahajan, D. R., 754
Mahoney, E. B., 730
Mahony, D. V., 783
Maksad, A. K., 711
Mallos, A. J., 704, 751
Malm, J. R., 801
Maloney, J. V., Jr., 769
Mandelbaum, I., 810
Manfredi, F., 783, 803
Mann, G., 710
Manning, J. A., 716
Manulat, P. E., 707, 766, 767
Manzoli, U., 722
March, H. W., 784
Marshall, H. W., 702
Martt, J. M., 711, 784, 840
Mason, D., 722, 785
Mason, H. L., 707, 710, 722, 755
Mason, J. C., 722
Massaro, G. D., 748
Massie, E., 708
Masson, G. M. C., 707, 785
Mathieson, D. R., 707, 755
Mattox, V. R., 707, 755
Maxwell, M. H., 707, 785
Mayer, G. A., 735, 736, 839
Mazur, J. H., 840
McAfee, J. G., 704, 828
McCaffrey, M. H., 699, 749
McCaughan, D., 831
McCluer, R. H., 786
McCormick, E. C., 786
McCue, C. M., 786
McEachen, J. A., 706, 787
McGaff, C. J., 700, 790
McGinnis, K., 837
McGinty, J. T., 701, 798
McGregor, M., 787
McIlroy, M. B., 698
McIntosh, H. D., 708, 759, 787, 823
McKusick, V. A., 703, 834
McPherson, H. T., 793
Mead, J., 708
Meckstroth, C. V., 700, 727, 802
Meihaus, J. E., 711, 770, 839
Meissner, G. F., 701, 788
Mendelsohn, D., 839
Mendiola, R. P., 788
Mendlowitz, M., 706, 707, 788
Meneely, G. R., 703
Merendino, J., 748
Merrill, J. M., 827
Messer, J. V., 704, 778, 789, 827
Meyer, B. W., 757
Miller, A. J., 710, 789
Miller, B. F., 831
Miller, B. S., 830
Miller, D. B., 705, 767
Miller, F. A., 788
Miller, J. M., 699, 703, 789
Miller, R. A., 705, 795
Miller, W., 709, 817
Millikan, C. H., 811
Milliken, M. A., 722
Mills, D., 699, 796
Milnor, W. R., 700, 704, 790
Minor, J. B., 790
Mitchel, B. F., 711, 714
Moe, G. K., 698, 710
Moehring, C. C., 701, 788
Mior, T. W., 708, 790
Molnar, W., 700, 706, 802, 834
Moretz, W. H., 838
Morgan, B. C., 726
Morris, G. C., Jr., 705, 708, 711, 738, 791, 839
Morrow, A. G., 704, 752
Moscovitz, H. L., 757
Moses, C., Jr., 701
Moss, M., 804
Mostyn, E. M., 731
Moyer, J. H., 702, 706, 728, 791, 837
Mozley, J. M., 704, 828
Muller, O. F., 722, 724
Muller, W. H., Jr., 823
Murphy, D. R., 755
Murrah, P., 707

Nadas, A. S., 702, 705, 761, 776, 826
Naftchi, N., 707, 788
Nahas, G. G., 709, 839
Nakvanich, P., 707, 767
Navarre, J. R., 754
Neel, R. G., 791
Neill, C. A., 705, 816
Neill, W. A., 704, 778, 789, 827
Nelson, P. W., 761
Neufeld, H. N., 699, 792
Nichol, A. D., 792, 839
Nichols, H. T., 792
Noon, G. P., 761
Nothman, M. M., 699, 792
Novack, P., 793

Obenour, R. A., 710, 793
O'Connor, R. A., 777
Oldenburg, F. A., 792, 839
Olson, R. E., 703, 710
Omae, T., 707, 785
O'Moore, D., 791
O'Neal, R. M., 710
Ongley, P. A., 806
Opie, L., 710, 809
Ordway, N. K., 706, 755
Orgain, E. S., 704, 708, 719, 742, 759, 787, 793
Ormand, R., 840
Orvis, A. L., 707, 755
Osborn, J. J., 706, 753, 754
Osterkamp, R. W., 712
O'Sullivan, D., 841
Owen, C. A., Jr., 817

Page, I. H., 704, 710, 753, 803
Paine, C. M., 710, 750
Paley, H. W., 700, 739, 794, 799
Palmer, T. E., 738
Papaioannou, A. C., 699, 794

Parkerson, W. T., 803
Parkin, T. W., 721
Parlin, W., 709, 822
Parrish, A., 748
Parsons, W. B., Jr., 795
Pascuzzi, C. A., 817
Paton, B. C., 711, 795
Patterson, J. L., Jr., 703, 829
Paul, M. H., 705, 795
Paul, O., 708
Pearson, R. J., Jr., 840
Peeler, R. G., 800
Peirce, G., 804
Perloff, D., 814
Perry, D., 813
Peters, R. M., 760
Peterson, L. H., 702, 708
Pfaff, W. W., 704, 752
Piccrillo, R. T., 782
Pick, A., 700, 769, 775, 796
Pick, R., 710, 789
Piera, J., 704, 711, 719, 819
Pierson, R. N., Jr., 731
Pierucci, L., Jr., 711, 720
Pifer, C. L., 813
Pilgeram, L. O., 699, 796
Pollack, H., 703, 707, 709, 710
Pollak, O. J., 698
Pontius, R. G., 796, 797
Porter, R. R., 797
Potts, W. J., 839
Poutasse, E. F., 703
Pratt, G. H., 754
Pressman, R. S., 712
Prinzmetal, M., 777, 797
Proger, S., 699, 792
Puchner, T. C., 699, 709, 822

Quinlan, C. B., 720
Quiroz, A., 704, 766

Rabino, M. D., 705, 797
Ramirez, G., 805
Ramelkamp, C. H., Jr., 700
Ratz, L. A., 699, 700
Rasmussen, R. A., 699, 833
Rawan, R. S., 779
Rathbun, M. L., 716
Ratnoff, O., 702
Rausch, N. H., 704, 768
Read, R. C., 798
Redo, S. F., 702
Regan, T. J., 701, 798
Reichel, F., 704, 714
Reimer, S. M., 701, 740
Remington, R. D., 768
Renfro, N. L., 799
Reusch, C. S., 716
Riker, W. L., 839
Rinzler, S. H., 799
Rivara, G. L., 752
Roberts, E., 722
Robin, E. D., 706, 818
Robinson, M. J., 803
Robinson, S., 706, 754
Rockney, R. E., 707, 785
Rodbard, S., 799
Rodriguez, F. L., 701, 717
Roe, B. B., 800
Roe, R. D., 701, 800
Roehll, W. H., 800
Rogers, W. M., 711, 801
Roos, A., 708
Rosa, L. M., 801
Roseman, D. M., 783
Rosenblat, M., 726
Ross, J., Jr., 710, 728, 751
Ross, R. S., 801, 821
Rossi, P., 722, 771
Roth, G. M., 704
Rothfeld, E. L., 802
Rowlands, D. T., Jr., 751
Rowlatt, U. F., 706, 777
Rubin, A., 703
Rudolph, A. M., 705, 761, 776 802, 826
Rumble, L., Jr., 790
Runco, V., 700, 802
Rutstein, D. D., 700
Ryan, J. M., 700, 706, 727, 802, 834
Ryan, T. J., 765

Sackner, M. A., 803
Sader, A. A., 753
Sahay, B. M., 832, 833
Saidi, F., 805
Saltzman, H. A., 710, 793, 803
Salvo, R. C., 707, 767
Samet, C. M., 699, 724
Samet, P., 701, 811
Sampson, J., 702
Sandberg, H., 721, 740, 743, 825
Sanders, J., 840
Sandler, H., 741
Santiago, L. S., 766
Saslaw, M. S., 703, 804
Saul, M., 804
Sawyer, P. N., 710, 804
Sayen, J. J., 804
Sayman, A., 784
Scannell, J. G., 805, 829
Schaefer, L. E., 805
Schepers, G. W. H., 703
Scherbel, A. L., 805, 840
Scherlis, S., 708
Schiebler, G. L., 806
Schoenfeld, M. R., 775
Schraeder, J., 721, 825
Schram, A. C., 699, 796
Schweitzer, M. D., 753
Scott, R. F., 806
Sealy, W. G., 711, 759
Seegers, W., 699, 812
Seidell, M. A., 772
Sekelj, P., 787
Sellers, R. D., 705, 781
Selvester, R. H., 705, 734, 761, 806
Selzer. A., 784, 807
Sepulveda, G. D., 807
Serratto, M., 731
Shabetai, R., 807
Shainoff, J. R., 710, 808
Shanoff, H. M., 701, 800
Shapiro, A. P., 707, 808
Shapiro, M. J., 770
Shaw, D. M., 699, 772
Shearn, M. A., 809
Shenkin, H. A., 793
Sherber, D. A., 809
Shickman, M. D., 837
Shimamoto, T., 709, 809, 840
Shipp, J. C., 710, 809
Shirey, E. K., 710, 815
Shock, N., 840

Shugoll, G. I., 840
Shumacker, H. B., 810
Shumacker, H. B., Jr., 810
Siegel, A. C., 699, 700, 811, 835
Sieker, H. O., 710, 783, 793, 803
Siekert, R. G., 702, 811
Sigmann, J. M., 819
Silver, D., 837
Silverman, L. M., 701, 811
Simandl, I., 801
Simonson, E., 812
Simpson, R., 699, 821
Sims, E. A., 706, 774
Singleton, R., 712
Singleton, R. T., 725
Sipple, J., 718
Sirak, H. D., 706, 812, 834
Sise, H., 704, 772
Sive, E. B., 812
Sklarin, B. S., 699, 812
Sklaroff, D. M., 701, 723
Slade, H. D., 813
Sleator, W., Jr., 826
Sleeper, J. C., 708, 787, 823
Sleight, W. C., 838
Slocum, H. C., 839
Slodki, S. J., 813
Smith, E., 712
Smith, R. T., 706, 787
Smithwick, R. H., 704, 772
Smulyan, H., 701, 744, 813
Sobin, S. S., 840
Sodi-Pallares, D., 703
Sokolow, M., 814
Soloff, L. A., 703, 814, 815
Sommer, L. S., 815
Sones, F. M., Jr., 703, 704, 710, 753, 815
Spagnuolo, M., 747
Spain, D. M., 702, 816
Spencer, F. C., 705, 816
Spiekerman, R. E., 710, 816
Spittel, J. A., Jr., 817
Spitzer, J. J., 701, 723
Spotts, R. R., 704, 759, 763
Spring, M., 817
Stamler, J., 703, 709, 817
Stanfield, C. A., 707, 835
Stanton, R. E., 818
Starr, I., 703
Stead, E. A., Jr., 698, 713
Steiger, Z., 704, 715, 717
Stein, M., 706, 818
Stein, S. W., 765, 778
Steinbaum, H., 710, 804
Steinberg, A. G., 805
Steinberg, C. A., 824
Steinberg, I., 703, 745, 818
Stephenson, R. E., 704, 829
Stern, A. M., 819
Stevenson, H. E., 703
Stillerman, M., 699, 724, 819
Stollerman, G. H., 699, 700, 703, 811
Straus, R., 701, 773
Strehler, B. L., 840
Strole, D. G., 715
Stuckey, J. H., 704, 709, 711, 719, 762, 819
Suarez, E., 705, 767
Sudrann, R. B., 841
Suh, S. K., 820
Sunico, R., 706, 755
Surawicz, B., 706, 774
Surtshin, A., 772
Sutton, G. C., 763
Swan, H., 706, 711, 795
Swedlund, H. A., 702, 820

Tabatznik, B., 708, 820, 821
Taber, R. E., 705, 821, 840
Takagi, H., 707, 741
Talner, N. S., 819
Taranta, A., 699, 821
Taveras, J. M., 708
Taylor, H. L., 699, 709, 822
Taylor, W. J., 737
Templeton, J. Y., III, 711, 720
Templeton, M., 709, 817
Theilen, E. O., 700, 749
Thomas, C. B., 709
Thomas, W. A., 806
Thompson, H. K., Jr., 708, 787, 823
Thompson, J. H., Jr., 817
Thompson, W. M., Jr., 823
Thomson, G. W., 823
Thrower, W. B., 824
Titus, J. L., 699, 792
Tolles, W. E., 824
Toronto, A. F., 704, 829
Tremer, H., 840
Trocchi, A. L., 824
Trout, R. G., 825
Tsitouris, G., 721, 825
Tuckman, J., 825
Turino, G. M., 700, 826
Turner, J. D., 805
Tuttle, W. B., 709, 735
Tziros, D., 838

Urdanetta, E., 780
Uricchio, J. F., 792
Usman, A., 785

Valmont, I., 710, 804
Van Allen, M. W., 708
Van der Hauwaert, L. G., 826
Van Itallie, T., 707
Van Ness, A. L., 710, 773
Varco, R. L., 705, 781
Veasy, L. G., 704, 829
Venerose, R. S., 711, 762, 819
Vichayanonda, V., 766
Vick, J., 798
Vineberg, A. M., 703
Voege, N., 826
Vogel, J. H. K., 827
Vollenwieder, H., 711, 720
Voudoukis, I. J., 815

Wachtel, F. W., 802
Wagman, R. J., 704, 778, 789, 827
Wagner, H. N., Jr., 704, 828
Waldorf, D. S., 701, 765
Wallace, J. M., 828
Walther, R., 704, 772
Wang, Y., 829
Wansker, W. C., 790
Wareham, E. E., 705, 734
Warner, H. R., 704, 829
Warren, J. V., 700, 707, 739, 794
Wasserman, A. J., 829
Watkins, D. H., 830
Wegner, S., 837

Weil, M. H., 716, 830, 841
Weinberg, M., Jr., 715
Weirich, W. L., 704, 708, 759, 763, 800
Weissler, A. M., 711, 750, 800, 823, 828
Wells, R., Jr., 733
Wennemark, J. R., 710, 831
Wessler, S., 701, 706, 740, 818
West, J. W., 722
West, T. C., 779
Westersten, A., 701, 718
Wexler, B. C., 831
Wheat, M. W., 737
Whisnant, J. P., 811
White, P. L., 707
Whitelaw, G. P., 704, 772
Whitner, V. S., 720
Whittemore, R., 706, 755
Wikingsson, M. B., 722
Wilburne, M., 837
Williams, C., 831
Williams, T. W., 841
Willman, V. L., 705, 832
Wilson, W. R., 700, 749
Winer, B. M., 832, 833
Winter, C. C., 707, 785
Wissler, R. W., 699, 833
Wolf, R. L., 707, 788
Wolf, S. G., 703
Wolf, S. G., Jr., 841
Wolff, J. A., 700, 826
Wood, E. G., 791
Wood, E. H., 703, 708, 721, 806
Wood, H. F., 699, 700, 821
Wood, J. E., 834
Wooley, C. F., 706, 834
Wright, I. S., 702, 705, 780
Wurm, M., 701, 773
Wyman, M. G., 830

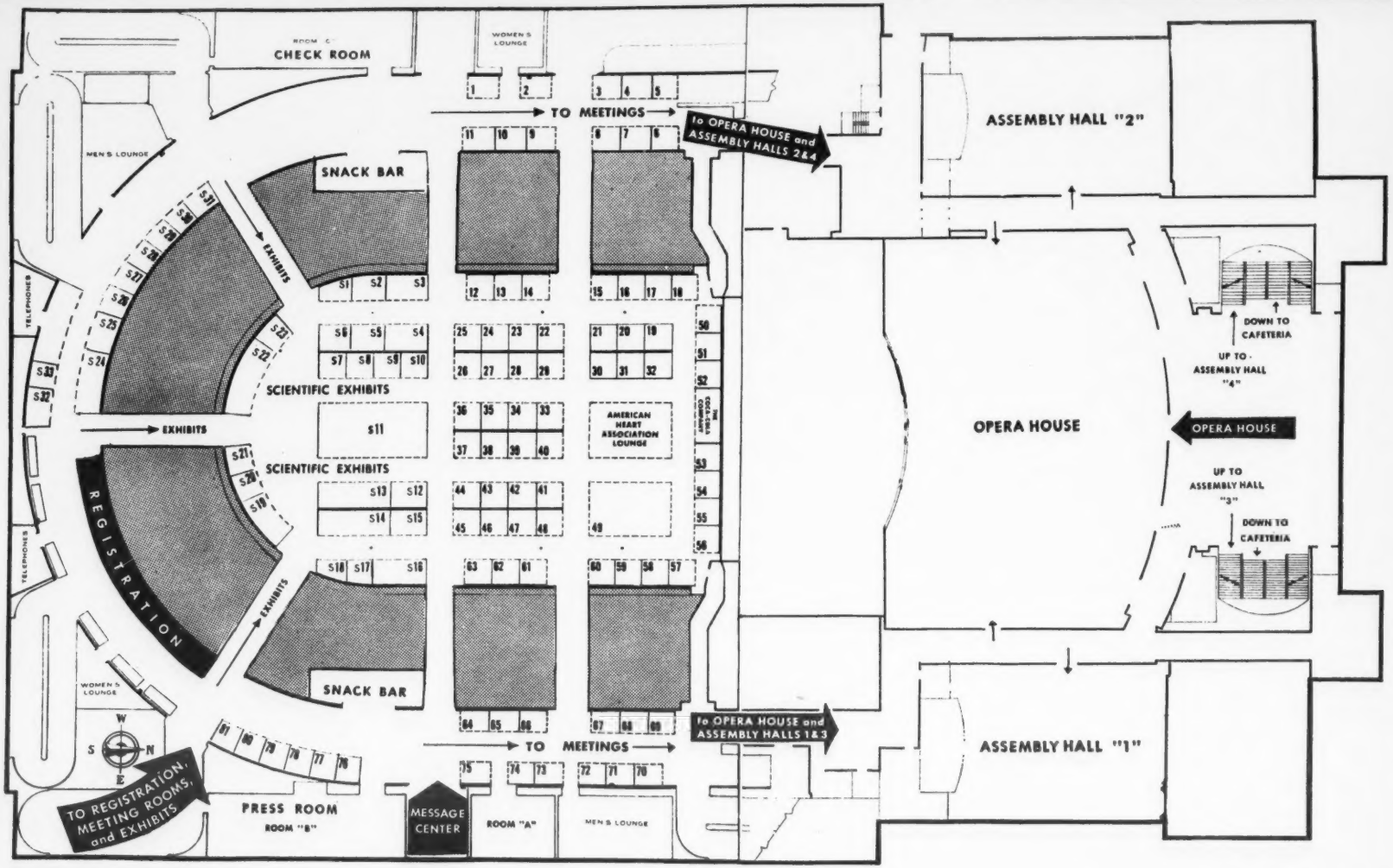
Yarashus, D. A., 700, 835
Yildiz, M., 723
Yoffee, H. F., 764
Youmans, W. B., 710, 835
Young, R. B., 786
Yu, P. N., 707, 730, 835

Ziegler, R. F., 758
Zimmerman, H., 702
Zimmerman, H. A., 705, 770, 836, 839
Zoll, P. M., 703, 727, 781

Industrial Exhibitors

1960 American Heart Association Meeting

	Booth Number
Armour Pharmaceutical Company	11
C. R. Bard, Inc.	27
Becton, Dickinson and Company	57
Birtcher Corporation	38
Blakiston Division McGraw-Hill Book Co.	18
Bowen & Company, Inc.	22
Burdick Corporation	29
Burroughs Wellcome & Co. (U.S.A.) Inc.	45
Burton, Parsons & Company	65
Cambridge Instrument Company, Inc.	31 & 32
Carnation Company	23
Ciba Pharmaceutical Products Inc.	25
Coca-Cola Company	Special Area
Coreo Incorporated	15
Cordis Corporation	81
Corn Products Company Best Foods Division	58
Custom Engineering and Development Company	75
Dallons Laboratories, Inc.	14
Davies, Rose & Company, Ltd.	74
F. A. Davis Company	72
Electrodyne Company, Inc.	46
Electronics for Medicine, Inc.	33 & 34
Endo Laboratories Inc.	56
Enseo, Incorporated	7
Foregger Company, Inc.	67
E. Fougera & Co., Inc.	21
Geigy Pharmaceuticals	63
General Diagnostics Division Warner-Chilcott	68
General Foods Kitchens	61
Gilford Instrument Laboratories Inc.	20
Grune & Stratton, Inc.	48
Hiss Pharmacal Company	3
Paul B. Hoeber, Inc.	66
Info-Dex Heart Registry System Medical Case History Bureau	79
Instrumentation Associates, Inc.	70
Ives-Cameron Company	9
Keleket X-Ray Corporation	8
Thos. Leeming & Co., Inc.	13
Eli Lilly and Company	39 & 40
Maico Electronics, Inc.	10
Mallinckrodt Chemical Works	78
Medtronic, Inc.	77
Merck Sharp & Dohme	35 & 36
Wm. S. Merrell Company	4 & 5
Micro X-Ray Recorder, Inc.	43
C. V. Mosby Company	55
North American Philips Co., Inc.	49
Ortho Pharmaceutical Corporation	19
Picker X-Ray Corp.	50 & 51
Reis Biologicals, Inc.	42
Riker Laboratories, Inc.	64
Roche Laboratories	16 & 17
Sanborn Company	53 & 54
Sandoz Pharmaceuticals	28
W. B. Saunders Company	12
Schering Corporation	6
Schick X-Ray Co., Inc.	1
Schwarzer Company	73
G. D. Searle & Co.	41
E. R. Squibb & Sons	30
Statham Instruments, Inc. of Puerto Rico	24
U. S. Catheter & Instrument Corp.	26
Walker Laboratories	52
Wallace Laboratories	59 & 60
Warner-Chilcott Laboratories	69
Waters Corporation	71
Wesson Oil	80
Winthrop Laboratories	47
Wyeth Laboratories	37 & 44
Wynn Pharmacal Corporation	76
Year Book Publishers, Inc.	2


CHECK ROOM
WOMEN'S LOUNGE
MEN'S LOUNGE
TO MEETINGS
to OPERA HOUSE and ASSEMBLY HALLS 2&4
ASSEMBLY HALL "2"
SNACK BAR
EXHIBITS
SCIENTIFIC EXHIBITS
AMERICAN HEART ASSOCIATION LOUNGE
OPERA HOUSE
DOWN TO CAFETERIA
UP TO ASSEMBLY HALL "4"
UP TO ASSEMBLY HALL "3"
REGISTRATION
TELEPHONES
to OPERA HOUSE and ASSEMBLY HALLS 1&3
ASSEMBLY HALL "1"
TO REGISTRATION, MEETING ROOMS, and EXHIBITS
PRESS ROOM
ROOM "B"
MESSAGE CENTER
ROOM "A"